

12. A pharmaceutical composition comprising a therapeutically effective amount of a compound of Claim 1 and a pharmaceutically acceptable carrier.

REMARKS

Applicants will address each of the pending matters in this application in the order in which they appear in the Office Action of January 2, 2002.

Objection to the Abstract of the Disclosure

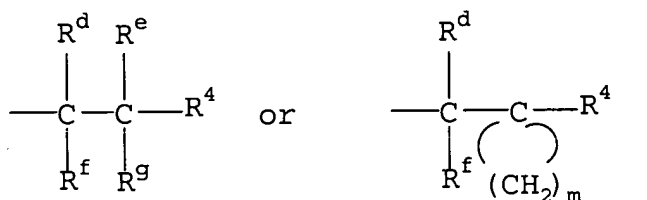
The Abstract of the Disclosure has been objected to for a number of grammatical and format reasons. By amendment herein, Applicants have corrected the appearance of the Abstract and respectfully ask that this objection be withdrawn.

Amino Acid Sequence Requirements under 37 CFR 1.821 through 1.825

The present application has been objected to for not complying with the amino acid sequence requirements of 37 CFR 1.821 through 1.825. Applicants enclose herein a completed amino acid sequence listing, as well as a computer-readable form thereof, to comply with the cited requirements.

Rejection of Claim 19 for Obviousness-Type Double Patenting

Claims 1 and 19 of the present application have been rejected under the judicially created doctrine of obviousness-type double patenting in view of Claims 1 and 13, respectively, of U.S. Patent No. 6,265,382, which issued from the parent application to the present application, U.S. Serial No. 09/331,876. In the parent application, a restriction requirement was given between the two variables for the moiety R², shown below:



In the parent application Applicants elected to prosecute the compounds of Group I in which R^2 is the first variable. By amendment herein Applicants have limited the compounds of Claim 1 to those of Group II in the original restriction requirement, which encompasses the compounds wherein R^2 is the second moiety shown above.

In view of the restriction requirement and Applicants amendments herein, removal of the rejection of Claims 1 and 19 for obviousness-type double patenting be withdrawn.

Rejection of Claims 19 and 25 under 35 U.S.C. 112, First Paragraph

Claims 19 and 25 have been rejected under 35 U.S.C. 112, first paragraph, for their inclusion of pharmaceutical uses. The rejection questions “the degree of criticality of the farnesyl transferase to the cell proliferation process.” Applicants respectfully disagree with the basis for this rejection because the clinical utility of farnesyl transferase inhibition has been established in the art.

As evidence of this understanding, Applicants enclose a copy of the article *Phase I and Pharmacokinetic Study of the Oral Farnesyl Transferase Inhibitor SCH 66336 Given Twice Daily to Patients With Advanced Solid Tumors*, Eskens et al., Journal of Clinical Oncology, Vol. 19, No. 4 (February 15), 2001: pp 1167-1175. The article describes the basis for use of farnesyl transferase inhibitors, as well as successful Phase I oral administration to humans of the farnesyl transferase inhibitor SCH 66336.

The utility of farnesyl transferase inhibitors is also discussed in the enclosed copies of the articles *Oral Chemotherapeutic Agents for Colorectal Cancer*, Sharma et al., The Oncologist, Vol. 5, No. 2, 99-107, April 2000, and *Novel Compounds in the Therapy of Breast*

Cancer: Opportunities for Integration with Docetaxel, Tolcher, The Oncologist, Vol. 6, Suppl 3, 40-44, June 2001. In their article, Sharma et al. describe farnesyl transferase inhibitors as follows (please see pages 6 and 7 of 15):

Farnesyltransferase Inhibitors

Ras proteins are normally associated with the inner surface of plasma membrane and act as intermediates in transmitting a wide variety of extracellular signals to the cytoplasm and the nucleus. *Ras* oncogenes are mutated in more than 40% of colonic adenocarcinomas and mutation leads to constitutive activation of *ras* [48]. Association of *ras* with the inner surface of plasma membrane is facilitated by farnesyl protein transferase (FPT), which modifies the cysteine residues on the protein. A variety of farnesyl transferase inhibitors is in clinical development and a selection of these oral agents are discussed below.

SCH66336

SCH66336 (Schering-Plough Research; Kenilworth, NJ) is a nonpeptidic small molecule with a tricyclic nucleus and is a potent and selective inhibitor of FPT. In preclinical studies, this compound inhibits growth of cell lines expressing mutated *K-ras*. In vivo studies have demonstrated that SCH66336 has potent antitumor activity against colon xenografts among many other types of implanted tumors in nude mice [49]. In two phase I trials [50, 51], SCH66336 was given orally twice daily as continuous administration or on a two of four-week schedule. The recommended phase II dose in both trials was 200 mg twice a day. The primary toxicities were diarrhea, anorexia, fatigue, and nausea. These toxicities were described as being mild and reversible on discontinuation of therapy. In the intermittent administration trial, two patients with colon cancer exhibited stable disease for four months. Recently, a continuous once-daily dosing trial was also reported [52]. An equivalent dose of SCH66336 (400 mg/day) was well tolerated on this schedule. Phase II trials are ongoing with

SCH66336 as a single agent in chemotherapy-resistant colorectal cancers, and phase I trials in combination with 5-FU are in progress.

R115777

R115777 (Janssen Research Foundation; Titusville, NJ) is an oral quinolone analog that inhibits farnesylation with consequent inhibition of growth of a variety of human tumor cell lines at nanomolar concentrations [53]. In human tumor xenografts of colon cancer, R115777 inhibited tumor growth without any overt toxicity [53]. Two phase I trials have been reported with this compound. In the first trial [54], R115777 was administered orally twice a day for 21 of 28 days. The recommended phase II dose on this schedule was 240 mg/m² as a twice daily dose. The principal toxicities were myelosuppression (neutropenia and thrombocytopenia), fatigue, and confusion. Plasma levels at the well-tolerated dose were equivalent to concentrations required for in vitro activity. In the second trial, R115777 was administered twice daily for five days every two weeks [55]. This regimen was not very myelosuppressive, but nausea, vomiting, headache, fatigue, and neuropathy were observed. A phase I trial combining chronic daily administration of R115777 along with bimonthly 5-FU and leucovorin administration has also been reported in patients with colorectal or pancreatic cancer [56]. Myelosuppression was the principal toxicity and final results are awaited regarding a recommended phase II dose in these patients.”

The Tolcher article similarly describes the clinical utility of farnesyl transferase inhibitors in the treatment of cancer (please see pages 3 and 4 of 10). At page 3 of 10, fourth paragraph, Tolcher also notes “Several farnesyl transferase inhibitors (FTIs) are in clinical development. They include the orally bioavailable agents R115777 and SCH 66336 and the oral and i.v. agent BMS 214662 [37-39].”

Applicants respectfully submit that one skilled in the art understands the pharmacological basis for the clinical utilities of the present invention. Further, the description

of the compounds and therapeutically effective doses in the present specification meet the disclosure requirements of 35 U.S.C. 112, first paragraph. In view of the foregoing, Applicants respectfully ask for reconsideration and withdrawal of this rejection.

Rejection of Claims 1-19, 19, 24 and 25 under 35 U.S.C. 112, Second Paragraph

Claims 1-19, 19, 24 and 25 have been rejected under 35 U.S.C. 112, second paragraph. Claim 1 is rejected for its use of the word “compounds” instead of the singular “compound” and the use in the corresponding dependent claims of “a compound”, rather than “the compound”. By amendment herein, Applicants have corrected the appearance to read “A compound”. Similarly, Applicants have corrected the dependent claims to read “the compound”.

Claim 1 has also been questioned for ending with the passage “and the pharmaceutically acceptable salts and prodrugs thereof.” Applicants have amended this passage to read “or a pharmaceutically acceptable salt or prodrug form thereof.”

Claim 19 was originally written with reference to a composition with no carrier mentioned. Claim 19 has been rewritten to include the requirements of a pharmaceutically acceptable carrier and a therapeutically effective amount of the compound in question.

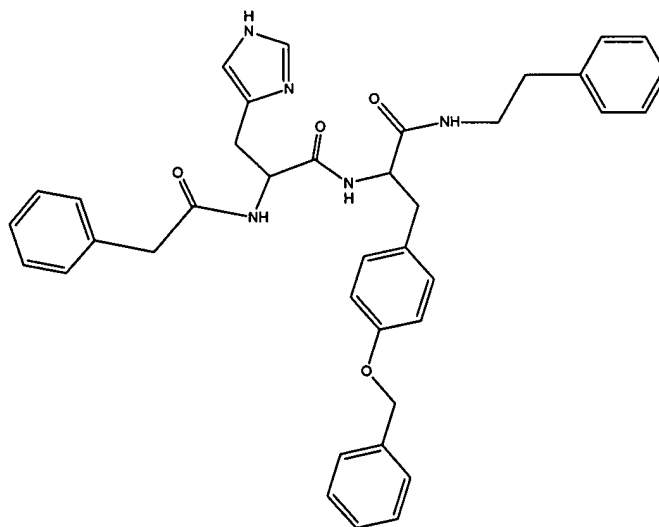
Claim 25 has been questioned for the passage “for use as a pharmaceutical.” As the subject matter of Claims 24 and 25 falls within the scope of amended Claim 19, Applicants have deleted Claims 24 and 25.

Applicants believe these amendments have addressed the reasons behind this rejection under 35 U.S.C. 112, second paragraph, and respectfully ask that it be withdrawn.

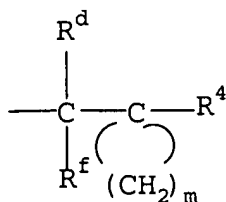
Rejection of Claims 1, 2, 5, 7 and 19 under 35 U.S.C. 102(e) over U.S. Patent No. 5,830,868 (Bolton et al.)

Claims 1, 2, 5, 7 and 19 have been rejected under 35 U.S.C. 102(e) as anticipated by Compound No. 26 in Column 19 of U.S. Patent No. 5,830,868 (Bolton et al.). Applicants respectfully disagree with this rejection.

The rejection states that the Bolton et al. compound, listed as “PhCH₂CO-D-His-Tyr(Obn)CONHCH₂CH₂Ph” does not anticipate the compounds of the present invention. Applicants submit the initial “CO” of the name indicates a carbonyl group, rather than a compound in which the variable “Y” is O, as mentioned in the present rejection. The compound listed by Bolton et al. would appear as:



Applicants also wish to note that the other end of the cited compound No. 26, listed as “-CONHCH₂CH₂Ph” would not anticipate the compounds of amended Claim 1 wherein the moiety R² is limited carbocycle-containing groups of the formula:



In view of the differences between the compound disclosed by Bolton et al. and those of the presently claimed invention, withdrawal of this rejection under 35 U.S.C. 102(e) is respectfully requested.

In view of the foregoing, Applicants believe the present application is now in condition for allowance and respectfully solicit a decision to that effect.

Respectfully submitted,

Date: March 25, 2002

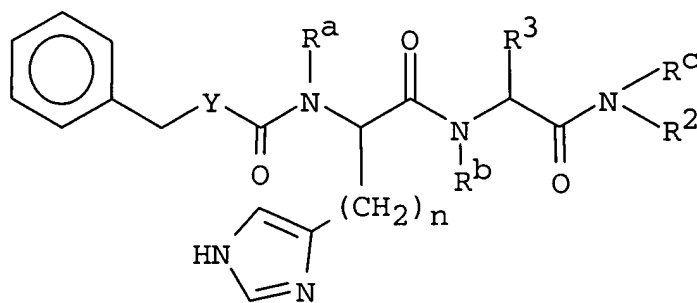


Steven R. Eck
Reg. No. 36,126
Patent Department
Warner-Lambert Company
2800 Plymouth Road
Ann Arbor, MI 48105
Tel: (734)-622-4040
Fax: (734)-622-1553

Enclosures: The Oncologist, Vol. 5, No. 2, 99-107, April 2000
The Oncologist, Vol. 6, Suppl 3, 40-44, June 2001
J. Clin. Oncology, Vol. 19, No. 4 (Feb. 15), 2001: pp 1167-1175

Marked-Up Copy of Amendments**ABSTRACT OF THE DISCLOSURE**

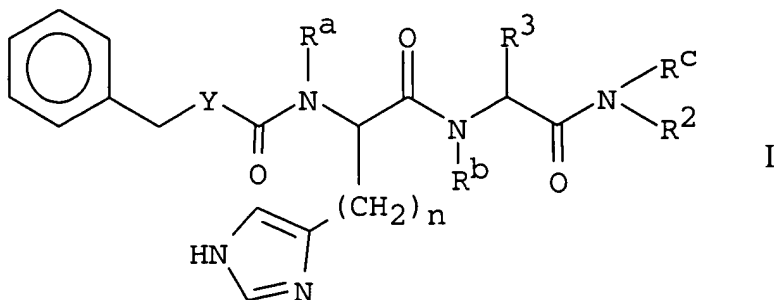
The present invention provides compounds having the structure represented by Formula I. [.]



[Also provided is a] and methods of treating cancer, restenosis, atherosclerosis, or psoriasis or preventing restenosis, and a pharmaceutical composition comprising a compound of Formula I and a pharmaceutically acceptable carrier.[.]

In the Claims

13. A [C]ompound[s] having the Formula I

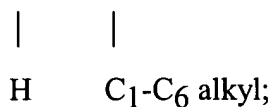


wherein:

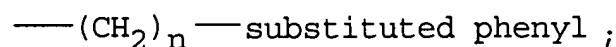
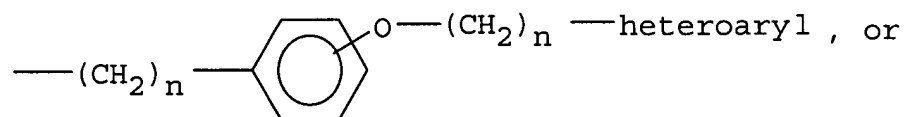
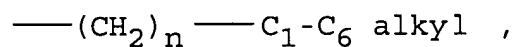
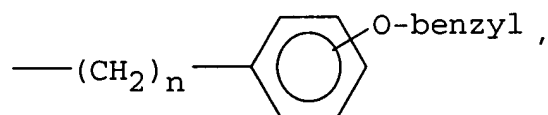
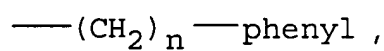
R^a , R^b , R^c are each independently C_1 - C_6 alkyl or hydrogen;

R^d , R^e , R^f , and R^g are each independently C_1 - C_6 alkyl, hydrogen, or phenyl;

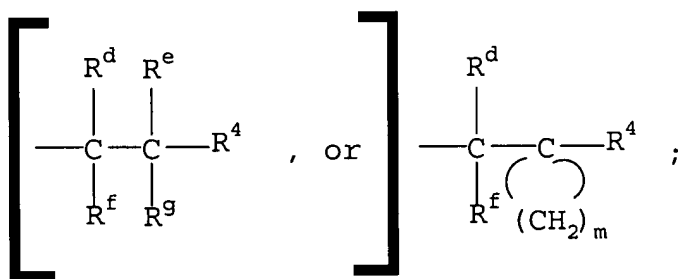
Y is -O-, -N-, or -N-;



R^3 is



R^2 is



R^4 is aryl, substituted aryl, or C_1 - C_6 alkyl; and

each n is independently 0 to 5, m is 2 to 4 [and the] or a pharmaceutically acceptable salt[s, and] or prodrug[s] form thereof.

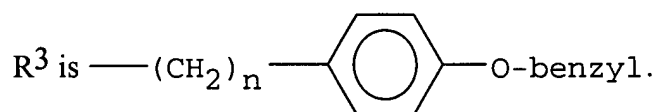
14. [A compound according to] The compound of Claim 1 wherein
Y is -O-.

15. [A compound according to] The compound of Claim 1 wherein
Y is -N- or -N-

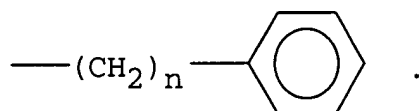
$$\begin{array}{cc} | & | \\ \text{H} & \text{CH}_3 \end{array}$$

16. [A compound according to] The compound of Claim 1 wherein R^a is hydrogen, R^b is
methyl,
and R^c is hydrogen.

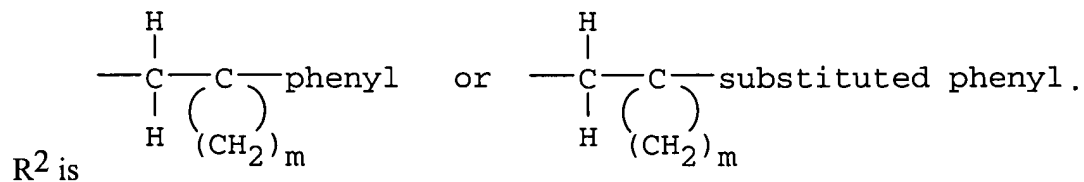
17. [A compound according to] The compound of Claim 1 wherein



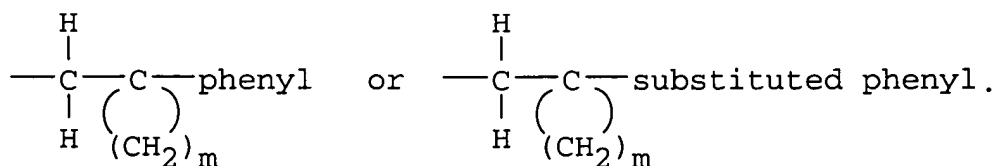
18. [A compound according to] The compound of Claim 1 wherein R³



19. [A compound according to] The compound of Claim 1 wherein



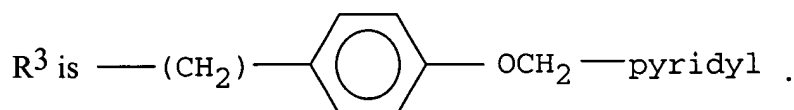
20. [A compound according to] The compound of Claim 9 wherein m of



m is 3 or 4.

21. [A compound according to] The compound of Claim 1 wherein R^3 is $-(CH_2)_n-C_1-C_6$ alkyl.

22. [A compound according to] The compound of Claim 1 wherein



23. The compounds:

$[[S-(R^*,R^*)]-[1-\{2-(4\text{-Benzyloxy-phenyl})-1-[2-(2\text{-fluoro-phenyl})\text{-ethyl-carbamoyl}]\text{-ethyl}\}-methyl\text{-carbamoyl}]-2-(3H\text{-imidazol-4-yl})\text{-ethyl}]\text{-carbamic acid benzyl ester};$

$[S-(R^*,R^*)]-[1-\{[2-(4\text{-Benzyloxy-phenyl})-1-(2\text{-pyridin-2-yl-ethyl-carbamoyl})\text{-ethyl}]\text{-methyl-carbamoyl}\}-2-(3\text{ H-imidazol-4-yl})\text{-ethyl}]\text{-carbamic acid benzyl ester};$

$[S-(R^*,R^*)]-[1-\{[2-(4\text{-Benzyloxy-phenyl})-1-(2,2\text{-diphenyl-ethylcarbamoyl})\text{-ethyl}]\text{-methyl-carbamoyl}\}-2-(3H\text{-imidazol-4-yl})\text{-ethyl}]\text{-carbamic acid benzyl ester};$

$[S-(R^*,R^*)]-[1-\{[2-(4\text{-Benzyloxy-phenyl})-1-(2\text{-phenyl-propylcarbamoyl})\text{-ethyl}]\text{-methyl-carbamoyl}\}-2-(3H\text{-imidazol-4-yl})\text{-ethyl}]\text{-carbamic acid benzyl ester};$

$[S-(R^*,R^*)]-[2-(3H\text{-Imidazol-4-yl})-1-\{methyl-[3\text{-methyl-1-(2-methyl-2-phenyl-propylcarbamoyl})\text{-butyl}]\text{-carbamoyl}\}\text{-ethyl}]\text{-carbamic acid benzyl ester};$

$[S-(R^*,R^*)]-[1-\{[2-(4\text{-Benzyloxy-phenyl})-1-(1\text{-methyl-2-phenyl-ethylcarbamoyl})\text{-ethyl}]\text{-methyl-carbamoyl}\}-2-(3H\text{-imidazol-4-yl})\text{-ethyl}]\text{-carbamic acid benzyl ester};]$

[S-(R*,R*)]-[1-({2-(4-Benzyloxy-phenyl)-1-[(1-phenyl-cyclopropyl-methyl)-carbamoyl]-ethyl}-methyl-carbamoyl)-2-(3H-imidazol-4-yl)-ethyl]-carbamic acid benzyl ester;

[[S-(R*,R*)]-[1-{[2-(4-Chloro-phenyl)-1-(2-methyl-2-phenyl-propylcarbamoyl)-ethyl]-methyl-carbamoyl}-2-(3H-imidazol-4-yl)-ethyl]-carbamic acid benzyl ester;

[S-(R*,R*)]-2-(3-Benzyl-ureido)-3-(3H-imidazol-4-yl)-N-methyl-N-{1-(2-methyl-propyl-carbamoyl)-2-[4-(pyridin-4-ylmethoxy)-phenyl]-ethyl}-propionamide;

[S-(R*,R*)]-[1-{{2-(4-Benzyloxy-phenyl)-1-(1-methyl-2-phenylethylcarbamoyl)-ethyl}-methyl-carbamoyl}-2-(3H-imidazol-4-yl)-ethyl]-carbamic acid benzyl ester;

[S-(R*,R*)]-(2-(3H-Imidazol-4-yl)-1-{methyl-[1-(2-methyl-2-phenyl-propylcarbamoyl)-2-p-tolyl-ethyl]-carbamoyl}-ethyl)-carbamic acid benzyl ester;

[S-(R*,R*)]-(2-(3H-Imidazol-4-yl)-1-{[2-(4-methoxy-phenyl)-1-(2-methyl-2-phenyl-propylcarbamoyl)-ethyl]-methyl-carbamoyl}-ethyl)-carbamic acid benzyl ester;

[S-(R*,R*)]-2-(3-Benzyl-ureido)-3-(3H-imidazol-4-yl)-N-methyl-N-[1-(2-methyl-2-phenyl-propylcarbamoyl)-2-phenyl-ethyl]-propionamide; and]

[S-(R*,R*)]-[1-[(2-(4-Benzyloxy-phenyl)-1-{[1-(2-fluoro-phenyl)-cyclopropylmethyl]-carbamoyl}ethyl)-methyl-carbamoyl]-2-(3H-imidazol-4-yl)-ethyl]-carbamic acid benzyl ester[.] ; and

[S-(R*,R*)]-[1-{{2-(4-Benzyloxy-phenyl)-1-[(1-phenyl-cyclobutylmethyl)-carbamoyl]-ethyl}-methyl-carbamoyl)-2-(3H-imidazol-4-yl)-ethyl]-carbamic acid benzyl ester;

24. A pharmaceutical composition [that] compris[es]ing a therapeutically effective amount of a compound of Claim 1 and a pharmaceutically acceptable carrier.



Phase I and Pharmacokinetic Study of the Oral Farnesyl Transferase Inhibitor SCH 66336 Given Twice Daily to Patients With Advanced Solid Tumors

By Ferry A.L.M. Eskens, Ahmad Awada, David L. Cutler, Maja J.A. de Jonge, Gré P.M. Luyten, Marije N. Faber, Paul Statkevich, Alex Sparreboom, Jaap Verweij, Axel-R. Hanauske, and Martine Piccart for the European Organization for Research and Treatment of Cancer Early Clinical Studies Group

Purpose: A single-agent dose-escalating phase I and pharmacokinetic study on the farnesyl transferase inhibitor SCH 66336 was performed to determine the safety profile, maximum-tolerated dose, and recommended dose for phase II studies. Plasma and urine pharmacokinetics were determined.

Patients and Methods: SCH 66336 was given orally bid without interruption to patients with histologically or cytologically confirmed solid tumors. Routine antiemetics were not prescribed.

Results: Twenty-four patients were enrolled onto the study. Dose levels studied were 25, 50, 100, 200, 400, and 300 mg bid. Pharmacokinetic sampling was performed on days 1 and 15. At 400 mg bid, the dose-limiting toxicity (DLT) consisted of grade 4 vomiting, grade 4 neutropenia and thrombocytopenia, and the combination of grade 3 anorexia and diarrhea with reversible grade 3 plasma creatinine elevation. After dose reduction, at 300 mg bid, the DLTs consisted of grade 4 neutropenia, grade 3 neurocortical toxicity,

and the combination of grade 3 fatigue with grade 2 nausea and diarrhea. The recommended dose for phase II studies is 200 mg bid, which was found feasible for prolonged periods of time. Pharmacokinetic analysis showed a greater than dose-proportional increase in drug exposure and peak plasma concentrations, with increased parameters at day 15 compared with day 1, indicating some accumulation on multiple dosing. Plasma half-life ranged from 4 to 11 hours and seemed to increase with increasing doses. Steady-state plasma concentrations were attained at days 7 through 14. A large volume of distribution at steady-state indicated extensive distribution outside the plasma compartment.

Conclusion: SCH 66336 can be administered safely using a continuous oral bid dosing regimen. The recommended dose for phase II studies using this regimen is 200 mg bid.

J Clin Oncol 19:1167-1175. © 2001 by American Society of Clinical Oncology.

IN MAMMALIAN CELLS, three functional *ras* genes are found. K-*ras*, N-*ras*, and H-*ras* genes encode for K-Ras, N-Ras, and H-Ras proteins, respectively. Ras is synthesized as a soluble and biologically inactive protein that undergoes several posttranslational modifications before being localized to the inner surface of the plasma membrane, where it exerts its activity as transducer of various extracellular growth-promoting stimuli. An essential step in the post-translational processing of Ras is farnesylation, the addition of a farnesyl or C₁₅ isoprenoid moiety from farnesyl diphosphate to the cysteine residue at the C-terminal side of Ras. Farnesyl transferase is the crucial enzyme in this process.¹⁻¹⁰ Mutations in one or more *ras* genes are frequently found in various human tumor types in variable incidence.^{3,8,10} Mutated *ras* oncogenes encode for oncoproteins that are synthesized in a way completely comparable to the synthesis of normal Ras. However, Ras oncoproteins are insensitive to the inhibitory activity of GTPase activating protein. As a result, cells harboring these Ras oncoproteins will show autonomous proliferation and malignant transformation.

As farnesylation of Ras oncoproteins is the essential enzymatic step in the process of posttranslational activation, inhibiting this step could theoretically result in the inhibi-

tion of this autonomous and malignant growth and proliferation. Thus, specific inhibitors of farnesyl transferase could possibly lead the way toward a specifically targeted treatment of *ras* oncogene-dependent tumor. Recently, however, evidence has emerged that the antiproliferative effects of farnesyl transferase inhibitors do not depend solely on inhibition of Ras and that the gain of alternate prenylated (geranylgeranylated) forms of the *Rho* protein *Rho-B* mediate cell growth inhibition.¹¹ Besides, when inhibiting farnesylation, it has to be taken into account that

From the Department of Medical Oncology, Rotterdam Cancer Institute (Daniel den Hoed Kliniek), Rotterdam; Department of Ophthalmology, University Hospital, Rotterdam; and NDDO Oncology, Amsterdam, the Netherlands; Institut Jules Bordet and European Organization for Research and Treatment of Cancer Early Clinical Studies Group, Brussels, Belgium; and Schering-Plough Research Institute, Kenilworth, NJ.

Submitted April 27, 2000; accepted October 4, 2000.

Address reprint requests to Ferry A.L.M. Eskens, MD, Department of Medical Oncology, University Hospital Rotterdam, PO Box 2040, 3000 CA Rotterdam, the Netherlands; email: eskens@oncd.azr.nl.

© 2001 by American Society of Clinical Oncology.
0732-183X/01/1904-1167

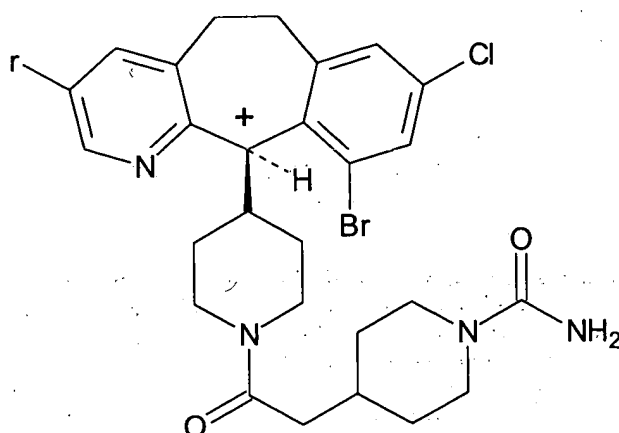


Fig 1. Chemical structure of SCH 66336.

this process is not restricted to Ras, as other cellular proteins also have to be farnesylated before exerting their activity.³

Several specific inhibitors of farnesyl transferase have been developed. SCH 66336 ((11R) 4[2[4-(3,10-dibromo-8-chloro-6,11-dihydro-5H-benzo[5,6] cyclohepta [1,2b]pyridin-11yl)-1-piperazinyl]-2-oxoethyl]-1-piperidinecarboxamide) (Fig 1) is a tricyclic nonpeptidyl, nonsulphydryl farnesyl transferase inhibitor. In vitro, it blocks farnesylation of H-Ras by purified human farnesyl protein transferase with an 50% inhibitory concentration (IC₅₀) of 1.9 nmol/L and farnesylation of K-Ras-4B with an IC₅₀ of 5.2 nmol/L. SCH 66336 blocks anchorage-independent growth of K-Ras-transformed rodent fibroblasts with an IC₅₀ of 0.4 μ mol/L and blocks the transformed growth properties (eg, anchorage-independent growth) of rodent fibroblasts that have been transformed with mutant *ras* and human tumor cell lines containing mutated *ras*.^{12,13} It does not inhibit geranylgeranyl protein transferase 1 in concentrations up to 50 μ mol/L. Anchorage-independent growth of various mutated K-*ras*-containing human tumor cell lines, such as HTB 177 lung carcinoma, A549 lung carcinoma, HCT 116 colon carcinoma, and HPAF II and MiaPaCa pancreatic carcinoma, is inhibited by SCH 66336 at concentrations of 0.5 μ mol/L, whereas the growth of the DLD-1 colon carcinoma cell line is inhibited at 3 μ mol/L. Interestingly, several human tumor cell lines that do not contain *ras* mutations, such as HTB 173 and HTB 175 lung carcinoma and MCF-7 breast carcinoma, are also sensitive to the growth-inhibitory effects of SCH 66336. This might be explained in part by the action of oncogenes or autocrine factors that lie upstream in the Ras signal transduction pathway. In vivo studies, SCH 66336 showed growth-inhibitory effects in human tumor xenografts, including DLD-1 and HCT 16 colon carcinoma, A549 and HTB 177 lung carcinoma, AsPc-1, HPAF-II, HS 700T and MiaPaCa pancreas carcinoma, and DU 145 prostate carcinoma.

Additionally, in a WAP-H-*ras* transgenic mouse model developing tumors of the mammary and salivary gland, dose-dependent tumor regressions have been recorded.¹⁴ Preclinical chronic oral toxicity studies revealed dose-dependent myelosuppression, weight loss, diarrhea, and vomiting in rats and monkeys (Schering-Plough Research Institute, Kenilworth, NJ, data on file).

This phase I and pharmacokinetic study represents the first administration of SCH 66336 in patients with advanced solid tumors using a continuous twice daily oral dosing regimen.

PATIENTS AND METHODS

Eligibility Criteria

Patients with a cytologically or histologically confirmed diagnosis of a solid tumor refractory to standard treatment or for whom no standard therapy was available were eligible for this study. Patients with primary CNS neoplasm, known brain or leptomeningeal metastases; or known bone marrow involvement were excluded. Further eligibility criteria included the following: age \geq 18 years; World Health Organization performance status of \leq 2; life expectancy of \geq 12 weeks; no anticancer therapy in the previous 4 weeks (6 weeks for nitrosoureas or mitomycin); no prior bone marrow or stem-cell transplantation; no known human immunodeficiency virus positivity or AIDS-related illness; adequate function of bone marrow (hemoglobin \geq 6.2 mmol/L, absolute neutrophil count \geq 1.5×10^9 /L, platelet count \geq 100×10^9 /L); liver (bilirubin \leq 25 μ mol/L; AST and ALT within 2.5 times the normal upper limit), and kidney (serum creatinine \leq 140 μ mol/L); ability to take oral medication; and no more than two prior combination chemotherapy regimens or one prior combination regimen plus two single-agent regimens. Local ethics boards approved the protocol and informed-consent brochures. All patients gave written informed consent at study entry.

Pretreatment Assessment and Follow-Up Studies

Before therapy, a complete medical history was taken and a physical examination was performed. A complete blood count, including WBC differential, and serum chemistry, including sodium, potassium, calcium, magnesium, phosphorus, urea, uric acid, creatinine, total protein, albumin, glucose, alkaline phosphatase, bilirubin, AST, ALT, gamma-glutamyl transpeptidase, and lactate dehydrogenase, were performed, as were urine analysis, ECG, and chest x-ray. Because some visual proteins (ie, rhodopsin kinase and transducin gamma) are known to undergo farnesylation, patients were referred for ophthalmologic examination including retinal photography before treatment, after 4 and 8 weeks, and bimonthly thereafter. Weekly evaluations included history, physical examination, toxicity assessment according to National Cancer Institute common toxicity criteria (version date December 1994), complete blood count, serum chemistries, urine analysis, and ECG. Tumor measurements were performed before treatment, at 4 and 8 weeks, and bimonthly thereafter and were evaluated according to the World Health Organization criteria for response.¹⁵ In case of progressive disease, patients were taken off study.

Drug and Drug Administration

SCH 66336 ((11R) 4[2[4-(3,10-dibromo-8-chloro-6,11-dihydro-5H-benzo[5,6] cyclohepta[1,2b]pyridin-11yl)-1-piperazinyl]-2-oxoethyl]-

1-piperidinecarboxamide) is a crystalline solid containing one chiral center. It was supplied as 25-, 100-, and 200-mg blue opaque gelatin capsules by Schering-Plough Research Institute. The capsules were swallowed immediately after breakfast and after supper, with approximately 240 mL of noncarbonated water. On days of pharmacokinetic sampling, patients were administered standardized meals immediately before drug administration. SCH 66336 was taken for 28 consecutive days and was continued in case of stable disease or disease remission after this period for as long as no disease progression and/or no unacceptable drug-related toxicity was seen. Routine antiemetics were not prescribed. SCH 66336 administration was immediately interrupted at the occurrence of dose-limiting toxicity (DLT).

Dosage and Dose Escalation

The starting dose of SCH 66336 was 25 mg bid. This dose was based on the safety results of the 15-mg/kg/d dose in 3-month toxicology studies in monkeys. Although this was not a "no-effect dose," the only findings in monkeys were increased liver weight. At the first day of treatment, patients were given a single dose for pharmacokinetic purposes.

Dose escalation was performed according to a schedule of dose doublings. At each dose level, a minimum of three patients had to have 28 days of treatment before escalation was allowed. Once DLT was seen in one patient at a given dose level, at least six patients had to be treated at that dose level before further dose escalation was allowed. DLT was defined as any \geq grade 3 nonhematologic toxicity or a serum creatinine elevation of \geq three times the upper limit of normal. Grade 3 fever in absence of infection and grade 3 nausea or vomiting in patients not receiving adequate antiemetic treatment were not considered DLT. Neutropenia or thrombocytopenia \geq grade 3 or grade 4 anemia constituted hematologic DLT. The maximum-tolerated dose was defined as the highest dose to be administered to a group of six patients producing tolerable, manageable, and reversible but DLT in at least two out of six patients. At the proposed dose for phase II studies, a maximum of one out of six patients was allowed to experience DLT. No inpatient dose escalation was allowed.

Pharmacokinetic Studies

For pharmacokinetic analysis, 6-mL blood samples were taken on day 1 via an intravenous cannula before administration, at 30, 60, and 90 minutes, and at 2, 4, 6, 8, 12, 14, and 24 hours after dosing. On day 14, a blood sample was taken before the evening dose; on day 15, blood samples were taken before the morning dosing, at 30, 60, and 90 minutes, and at 2, 4, 6, 8, and 12 hours after dosing, with the last sample to be taken before the evening dose. On day 16, a sample was taken before the morning dose. If patients were on treatment after three 28-day cycles, optional pharmacokinetic blood samples were again obtained. Blood samples were collected in sodium heparin tubes and were immediately centrifuged at 3,000 rpm for 15 minutes at 10°C, after which plasma was divided into two aliquots of at least 1 mL and frozen at -70°C until analysis. Plasma samples were assayed by a specific and sensitive high-performance liquid chromatography assay.¹⁶ The lower limit of quantitation of the assay was 1.0 ng/mL. SCH 66336 excretion in urine was measured on day 15 in urine samples collected from 0 to 6 and 6 to 12 hours after dosing. Urine samples were analyzed using the same validated high-performance liquid chromatography assay. For urine analysis, the lower limit of quantitation was 2.0 ng/mL.

For each patient, the area under the plasma concentration-versus-time curve (AUC) was calculated by the trapezoidal rule and extrapo-

lated to infinity by linear regression analysis. The apparent total-body clearance/F (F denotes the oral bioavailability fraction) was calculated as dose/AUC. The apparent volume of distribution at steady state ($V_{d,ss}/F$) was calculated by a noncompartmental method based on the statistical moment theory.¹⁷ The terminal disposition half-life was calculated by dividing 0.693 by the fitted rate constant for drug elimination from the central compartment, estimated by linear regression analysis of the final data points of the log-linear concentration-time plot.

Statistical Analysis

Interpatient differences in pharmacokinetic parameters were assessed by the coefficient of variation, expressed as the ratio of the SD and the observed mean. Pharmacokinetic parameters were analyzed as a function of the SCH 66336 dose level using the Kruskal-Wallis one-way analysis of ranks followed by Dunn's multiple comparison test for identifying statistically different groups. Variability in pharmacokinetics between administration days was evaluated by either the paired Student's *t* test after testing for normality and heteroscedasticity or the Wilcoxon test for matched pairs. Statistical calculations were performed using the Number Cruncher Statistical System 5.X series (J.L. Hintze, East Kaysville, UT). Statistical significance was considered to be reached at $P < .05$, with a two-tailed distribution. All data are presented as mean \pm SD, except where indicated otherwise.

RESULTS

Twenty-four patients (14 men and 10 women) with a median age of 56 years (range, 28 to 77 years) were enrolled onto the study. Patient characteristics are listed in Table 1. The median duration of treatment was 40 days (range, 5 to 280 days; mean, 63.4 days). Dose levels studied were 25 ($n = 4$), 50 ($n = 5$), 100 ($n = 3$), 200 ($n = 6$), 400 ($n = 3$), and 300 ($n = 3$) mg bid.

Hematologic Toxicity

Hematologic toxicities observed in this trial are listed in Table 2. Transient grade 1 neutropenia reversible without treatment interruption was seen in the fourth week and in the fourth month of treatment in one patient at 50 mg bid and in the first week and the second month of treatment in one patient at 100 mg bid. At 400 mg bid, grade 4 neutropenia lasting from day 14 to 28 was seen in one patient. Granulocyte colony-stimulating factor was administered from day 26 to 29. This patient also developed transient grade 4 thrombocytopenia after withdrawal of the study drug. At 300 mg bid, grade 4 neutropenia lasting from day 17 to 35 was seen in one patient. No granulocyte colony-stimulating factor was administered. Transient grade 1 thrombocytopenia was recorded in the third week of treatment in one patient at 25 mg and 300 mg bid, respectively. One patient at 300 mg bid developed grade 2 thrombocytopenia lasting 5 days after treatment had been stopped because of other toxicities. One patient at 400 mg bid developed grade 3 anemia 6 days after treatment had been stopped.

Table 1. Patient Characteristics

Characteristic	No. of Patients
No. of patients entered	24
No. of patients assessable	24
Male/female	14/10
Age, years	
Median	56.5
Range	28-77
WHO performance status	
Median	1
Range	0-2
0	9
1	12
2	3
Prior therapy	
None	5
Chemotherapy	8
Radiotherapy	3
Chemo- and radiotherapy	8
Primary tumor site	
Colorectal	5
Lung	3
Breast	2
Cervix uteri	2
Unknown primary	2
Liver	2
Miscellaneous	8

Abbreviation: WHO, World Health Organization.

Nonhematologic Toxicity

Major nonhematologic side effects observed in this trial are listed in Table 3. Toxicity was mainly gastrointestinal and consisted of watery diarrhea, nausea, vomiting, and anorexia. In patients with diarrhea, loperamide administered on an as-needed basis resulted in prompt relief of symptoms. At lower doses, vomiting was usually mild and required no specific treatment. Anorexia occurred mainly at the highest dose levels, was mild, and required no specific therapy. Other toxicities consisted of grade 1 or 2 elevation of liver enzymes and reversible grade 1 or 2 elevated plasma creatinine levels recorded at all dose levels studied. In one patient at 400 mg bid, grade 3 anorexia and diarrhea,

together with grade 2 nausea and grade 1 vomiting, resulted in grade 3 creatinine due to dehydration, defining DLT. Grade 1 weight loss was recorded in three patients at 200 mg bid and one patient each at 300 and 400 mg bid. Almost all patients who experienced weight loss had various concurrent gastrointestinal toxicities. Transient grade 2 fever was recorded in one patient at 300 mg bid who also developed transient grade 2 oral mucositis after SCH 66336 administration was interrupted because of other side effects. Atrial flutter/fibrillation was recorded in the third month of therapy in a single patient at 100 mg bid. This patient had a prior history of atrial fibrillation. Asymptomatic sinus bradycardia (55 beats/min) was recorded in the third week of treatment in one patient at 300 mg bid. A 24-hour Holter monitoring following the day of onset revealed numerous episodes of bradycardia. Nineteen days after discontinuation of the study drug because of other toxicities, 24-hour Holter monitoring showed no further episodes of bradycardia. Serial ECGs showed no relevant changes in any of the patients. Ophthalmologic examinations revealed no retinal changes.

DLT

Since in the first three patients at 200 mg bid no toxicity greater than grade 1 was recorded, the dose was doubled to 400 mg bid. At this dose, DLT was seen in three consecutive patients. It consisted of grade 4 vomiting in the first week of treatment in one patient, grade 4 neutropenia lasting 14 days that coincided with grade 4 thrombocytopenia lasting 5 days which occurred after 2 weeks of treatment in a second patient, and the combination of grade 3 diarrhea, grade 3 anorexia, grade 2 nausea, and grade 1 vomiting leading to reversible grade 3 elevation of plasma creatinine that occurred after the first week in a third patient. Three additional patients were then treated at the next lower dose level of 200 mg bid, but as no additional DLTs were recorded, it was decided to escalate the dose to 300 mg bid. At this dose, DLT was again observed in three consecutive patients, consisting of grade 4 neutropenia lasting 10 days and occurring after 3 weeks of treatment, reversible grade 3

Table 2. Hematologic Toxicity (worst per patient)

Dose Level (bid, mg)	No. of Patients	Neutropenia (CTC grade)				Thrombocytopenia (CTC grade)			
		1	2	3	4	1	2	3	4
25	4	—	—	—	—	1	—	—	—
50	5	1	—	—	—	—	—	—	—
100	3	1	—	—	—	—	—	—	—
200	6	—	—	—	—	—	—	—	—
400	3	—	—	—	1	—	—	—	1
300	3	—	—	—	1	1	1	—	—

Abbreviation: CTC, common toxicity criteria.

Table 3. Nonhematologic Toxicity (worst per patient)

Dose Level (bid, mg)	No. of Patients	Nausea (CTC grade)			Anorexia (CTC grade)			Diarrhea (CTC grade)				Vomiting (CTC grade)				Fatigue (CTC grade)			Neurocortical (CTC grade)			Creatinine (CTC grade)		
		1	2	3	1	2	3	1	2	3	4	1	2	3	4	1	2	3	1	2	3	1	2	3
25	4	—	—	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1	—	—
50	5	1	—	—	—	—	—	2	—	—	—	1	—	—	—	1	—	—	—	—	—	3	—	—
100	3	1	—	—	—	—	—	1	—	—	—	1	—	—	—	1	—	—	—	—	—	1	—	—
200	6	5	—	1	4	—	1	1	1	2	1	2	2	—	—	3	1	—	—	—	—	5	—	—
400	3	—	3	—	—	—	2	1	1	1	—	2	—	—	1	—	1	—	—	—	—	1	1	1
300	3	2	1	—	1	1	—	2	1	—	—	2	—	—	—	1	1	1	—	—	1	1	—	—

neurocortical toxicity consisting of disorientation and confusion in the first week of treatment, and the combination of grade 3 fatigue with grade 2 nausea and grade 2 diarrhea occurring in the third week of treatment. No patient at 400 mg bid or 300 mg bid was able to complete 28 days of treatment. The recommended dose for phase II trials was set at 200 mg bid. The six patients treated at this dose level received the drug for a median of 57 days (range, 52 to 280 days).

Pharmacokinetics

Pharmacokinetic studies were completed in all 24 patients. The plasma concentration-versus-time profiles of SCH 66336 were similar for all patients studied, with mean curves obtained at the tested SCH 66336 dose levels shown in Fig 2. The mean single-dose noncompartmental pharmacokinetic parameters of SCH 66336 after doses ranging from 25 to 400 mg are listed in Table 4. Significant interpatient variability in pharmacokinetic parameters was apparent at all dose levels. The absorption of the drug was relatively slow, and peak concentrations were reached between 2.7 and 8.0 hours after drug intake. Peak plasma concentrations as well as AUCs increased in a greater than dose-proportional manner (Fig 3A). A 16-fold increase in dose (from 25 to 400 mg) was associated with an increase in mean peak plasma concentration of approximately 56-fold and an increase in the AUC of approximately 200-fold. The apparent clearance of SCH 66336 decreased exponentially from $1,190 \pm 462$ mL/min at a dose of 25 mg to 101 ± 27.3 mL/min at 400 mg (Fig 3B), while the $V_{d,ss}/F$ decreased from 331 ± 27.0 L to 90.4 ± 22.4 L at the same dose levels. There was a trend to increasing plasma half-life with increasing dose that was statistically significant at the two highest dose levels ($P < .007$; Kruskal-Wallis test). The peak plasma concentrations (not shown) and AUC_{0-12} (Table 4) increased approximately two- to five-fold on repeated dosing in a dose-independent manner ($P = .103$; Kruskal-Wallis test), which is more than expected based on accumulation effects only ($P = .0016$; paired Student's *t* test). In contrast, the terminal disposition half-life (data not shown)

was comparable between days 1 and 15, although the mean difference reached borderline significance ($P = .04$; Wilcoxon test for matched pairs of 10 patients). This suggests that the dose dependency in apparent clearance does not arise primarily from factors associated with saturation of excretory routes. Steady-state concentrations of SCH 66336 were attained by days 7 to 14, with only minor inpatient variability in trough levels (median coefficient of variation, 15.5%; range, 6% to 60%). The cumulative urinary excretion of unchanged SCH 66336 was dose-independent and accounted for only less than 0.02% of the administered dose. The mean renal clearance, ie, the product of the dose-fraction excreted unchanged in urine and the apparent total body clearance, was estimated as 0.117 ± 0.0105 mL/min, suggesting that SCH 66336 is not cleared by renal processes.

Response

No partial or complete responses were seen. One patient with pseudomyxoma peritonei had stable disease for 9+ months, whereas one patient with metastatic follicular thyroid carcinoma had stable disease for 7 months with ongoing treatment.

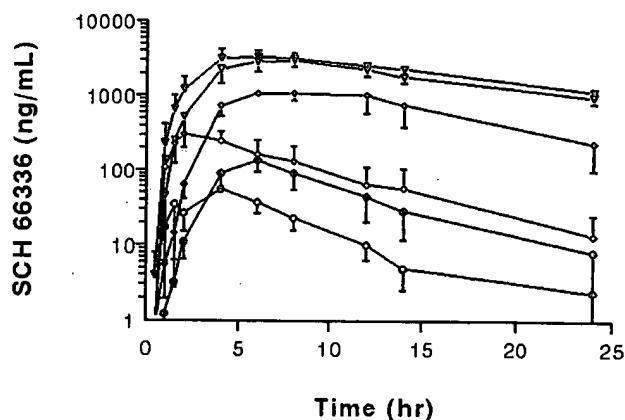


Fig 2. Plasma concentration-versus-time profiles of SCH 66336 in patients treated at a dose level of 25 mg (\square), 50 mg (\square), 100 mg (\diamond), 200 mg (\diamond), 300 mg (∇), or 400 mg (\star). Mean values (symbols) and SE (bar) are shown for all patients treated on day 1 at the indicated SCH 66336 dose level.

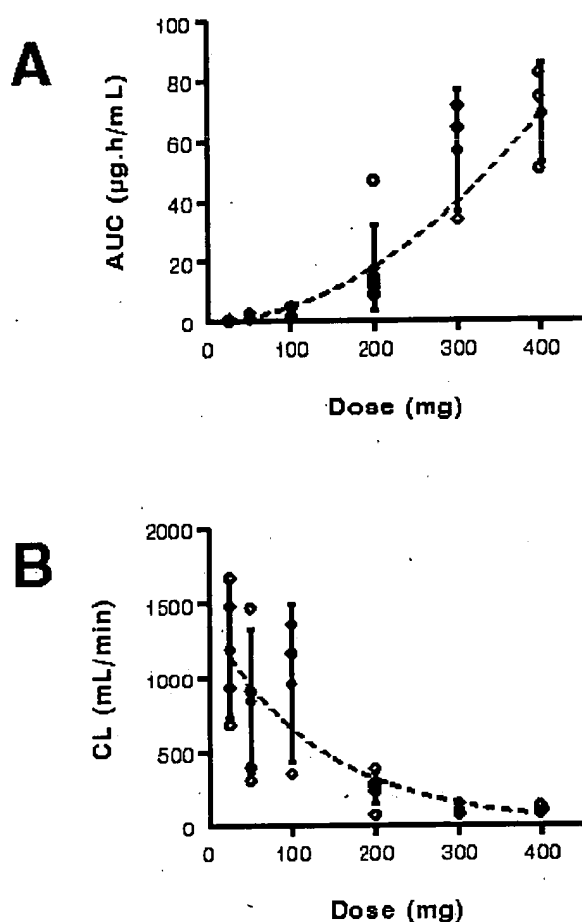


Fig 3. (A) Effect of dose on the AUC and (B) apparent clearance of SCH 66336 in 24 cancer patients. Closed symbols with error bars indicate mean values of the pharmacokinetic parameter at each of the tested dose levels and SD, respectively.

DISCUSSION

We performed a phase I and pharmacokinetic study to explore safety, tolerability, maximum-tolerated dose, and

pharmacokinetics of the oral farnesyl transferase inhibitor SCH 66336. In this study using continuous oral bid administration, side effects attributable to the study drug were hematologic and nonhematologic, whereas DLTs included neutropenia, thrombocytopenia, various gastrointestinal side effects, and neurocortical toxicity with reversible disorientation and confusion.

The hematologic toxicity of SCH 66336 in the current study consisted of dose-dependent, uncomplicated, and reversible neutropenia and thrombocytopenia occurring mainly at the two highest, nontolerable dose levels tested. At the dose level recommended for phase II studies, 200 mg bid, myelosuppression did not occur, even in the patient who was on treatment for up to 9+ months. This parallels the experience in three other studies using different dosing regimens of SCH 66336 in which hematologic toxicity was absent at these dose levels.¹⁸⁻²⁰ One of these studies also used a continuous treatment schedule.²⁰ This finding is in contrast to results obtained with other farnesyl transferase inhibitors. In two published reports on L-778,123, a peptidomimetic farnesyl transferase inhibitor given intravenously, myelosuppression comprised one of the DLTs and also occurred at dose levels recommended for further activity testing.^{21,22}

Out of three phase I studies²³⁻²⁵ that have been reported on the farnesyl transferase inhibitor R115777, myelosuppression comprised DLT in two,^{23,24} whereas in the third study, which used a 5 days on, 9 days off schedule, only minimal hematopoietic toxicity was observed.²⁵ In the only published phase I study with the novel farnesyl transferase inhibitor BMS-214662, exploring an intermittent treatment schedule, no myelosuppression was recorded.²⁶ Clearly, for farnesyl transferase inhibitors, myelosuppression is a class effect, with marked differences depending on agent and schedule of administration.

The nonhematologic side effects of SCH 66336 in our current study were predominantly gastrointestinal and con-

Table 4. Summary of SCH 66336 Pharmacokinetic Data

Dose Level (mg)	No. of Patients	C _{max} (ng/mL)	T _{max} (hour)	AUC (µg·h/mL)	T _{1/2} (hour)	CL/F (mL/min)	V _{d,ss} /F (L)	AUC _{d15/d1} *
25	4	63.9 ± 2.24	3.4 ± 1.3	0.397 ± 0.167	3.57 ± 1.32	1,190 ± 462	331 ± 27.0	2.65 ± 0.27
50	5	156 ± 96.1	5.2 ± 1.1	1.35 ± 0.955	3.68 ± 1.49	845 ± 486	460 ± 532	5.28 ± 1.83
100	3	333 ± 70.6	2.7 ± 1.2	2.46 ± 1.96	4.09 ± 1.29	958 ± 536	299 ± 114	3.66 ± 1.35
200	6	1,380 ± 728	6.7 ± 2.7	17.7 ± 14.4	5.45 ± 1.22	253 ± 103	114 ± 43.8	3.29 ± 0.56
300	3	2,900 ± 1,290	7.3 ± 1.2	56.4 ± 20.0	10.0 ± 0.59†	98.7 ± 42.9	85.4 ± 35.9	3.38 ± 1.60
400	3	3,610 ± 1,290	8.0 ± 5.3	69.1 ± 16.5	10.4 ± 0.25†	101 ± 27.3	90.4 ± 22.4	NA

NOTE: Data are expressed as mean values ± SD.

Abbreviations: C_{max}, peak plasma concentration; T_{max}, time to peak concentration; T_{1/2}, terminal disposition half-life; CL/F, apparent clearance; V_{d,ss}, apparent volume of distribution at steady-state; AUC_{d15/d1}, ratio of AUC₀₋₁₂ values measured on days 15 and 1, respectively.

*Dose-independent, *P* = .103 (Kruskal-Wallis test), but significantly different from 1, *P* = .0016 (paired Student's *t* test).

†Significantly different, *P* < .006 (Kruskal-Wallis test followed by Dunn's multiple comparison).

Table 5. Clinical Studies (single agent) of Farnesyltransferase Inhibitors; Schedule, DLT, Recommended Dose, Side Effects

Drug (ref)	Schedule	DLT	Recommended Dose (mg)	Side Effects at Recommended Dose
SCH 66336 ¹⁸	PO/bid d 1-7 q 3 weeks	Diarrhea, fatigue	350 bid	ANC, plts, N/V, diarrhea, fatigue
SCH 66336 ¹⁹	PO/bid d 1-14 q 4 weeks	Gastrointestinal	200 bid	N/V, diarrhea, fatigue
SCH 66336 ²⁰	PO/od continuous	Diarrhea	300 od	Diarrhea, N/V, renal, fatigue
L-778,123 ²¹	IV d 1-7 q 3 weeks	Q-Tc, neutropenia	560 (m ²) od	ANC, plts, N/V, somnolence, fatigue
L-778,123 ²²	IV d 1-14 q 3 weeks	Neutropenia, Q-Tc	560 (m ²) od	?
L-778,123 ²²	IV d 1-28 q 5 weeks	?	?	?
R115777 ²³	PO/bid continuous	Skin, neutropenia, thrombocytopenia, neuromotor/sensory	300 bid	Skin, ANC, plts, fatigue, N/V, neuro, dizziness
R115777 ²⁴	PO/bid d 1-21 q 4 weeks	Neutropenia, thrombocytopenia, confusion, fatigue, bilirubin	240 (m ²) bid	ANC, plts, fatigue, confusion
R115777 ²⁵	PO/bid d 1-5 q 2 weeks	Neuropathy, fatigue	?	?
BMS-214662 ²⁶	IV course 1	Hepatotoxicity	?	Fatigue, somnolence, gastrointestinal
	PO course 2 d 1 q 3 weeks	Gastrointestinal		

Abbreviations: PO, orally; bid, twice daily; od, once daily; IV, intravenously; d, day; q, every; Q-Tc, asymptomatic Q-Tc prolongation at ECG; ANC, absolute neutrophil count; plts, platelets; N/V, nausea and vomiting.

sisted of mild dose-dependent, noncumulative, and reversible diarrhea, vomiting, anorexia, and nausea. When diarrhea occurred at the recommended dose for phase II studies, treatment with loperamide always resulted in prompt and complete relief. Patients were advised to use loperamide on an on-demand basis, which always proved to be sufficient. At the recommended dose for phase II studies, vomiting was also usually mild and short-lasting and required no specific treatment. Anorexia and nausea occurred at virtually all dose levels and usually were mild. Gastrointestinal side effects were recorded in all studies of SCH 66336 and comprised DLT in all treatment schedules analyzed. This may suggest that gastrointestinal toxicity is not cumulative. Presumably partly related to these various gastrointestinal side effects, mild weight loss was noted in almost all patients. However, patients without gastrointestinal toxicity also experienced some weight loss that occurred mainly within the first 2 weeks of treatment. Remarkably, no additional weight loss was seen with ongoing treatment.

Nongastrointestinal side effects were diverse, infrequent, and usually mild. At the lower dose levels, noncumulative and reversible grade 1 creatinine increases were seen, but coinciding urine analysis never revealed any abnormality; therefore, we cannot rule out mild dehydration caused by various gastrointestinal side effects as the principal cause of these creatinine increases. In the patient at the nontolerable dose level 400 mg bid in whom grade 3 creatinine was recorded, urine analysis revealed no abnormalities and interruption of SCH 66336 dosing and intravenous rehydration resulted in a rapid and complete normalization of creatinine levels. In the present study, two episodes of

reversible atrial rhythm abnormalities (atrial fibrillation in a patient with previous cardiac history and asymptomatic sinus bradycardia) occurred, but serial ECGs did not show consistent changes in all other patients. This is in sharp contrast with the data from studies with L-778,123, in which prolongation of the Q-T time constituted DLT.^{21,22} In the current study, one episode of grade 3 rapidly reversible neurocortical toxicity consisting of disorientation and confusion was recorded, but no other episodes of either neurocortical toxicity or peripheral neuropathy were recorded in any of the other studies with SCH 66336. Reversible peripheral neurosensory and motor as well as central neurocortical toxicity have been described with oral R115777.²³⁻²⁵ No neuropathy was recorded with BMS-214662.²⁶

When considering which treatment schedule of SCH 66336 should preferably be used in future clinical trials, one should note that preclinical data demonstrate that SCH 66336 is a reversible competitive inhibitor of farnesyl transferase, and the biochemical effects are rapidly reversed on withdrawal of the compound. Because the compound thus is a competitive inhibitor, the schedule most likely to result in continuous inhibition of farnesyl transferase would be the continuous schedule. This schedule achieves the highest total dose and the longest exposure time.

When summarizing the results of the recorded toxicity profiles of the farnesyl transferase inhibitors that are currently being tested in clinical studies (SCH 66336, R115777 and L-778,123, and BMS-214662), one can conclude that myelosuppression is a common feature, whereas nonhematologic toxicities differ in essential ways. Table 5 lists the

results of the clinical studies with farnesyltransferase inhibitors presented to date.

This present study clearly demonstrates a dose dependency in SCH 66336 plasma pharmacokinetics in cancer patients, which contrasts with previous findings from pre-clinical dose-response studies. In the rat, peak plasma levels reached values of 3, 10, and 30 $\mu\text{mol/L}$ at oral doses of 10, 30, and 100 mg/kg, respectively.²⁷ In cancer patients, both the apparent clearance and the apparent $V_{d,ss}/F$ demonstrated a more than four- to 10-fold decrease at a dose of 400 mg, compared with 25 mg. The most likely explanation is an increase in F with multiple dose administration resulting in an apparent decrease in V_d and an apparent decrease in total-body clearance/ F . The opposing effects of these two processes on drug elimination leaves the apparent terminal disposition half-life almost dose-independent, except at the two highest dose levels. In addition, at repeated dosing, ie, when comparing the mean drug exposure and peak plasma concentrations of the various dose levels tested at day 15 with those of day 1, substantial increases were found that were greater than predicted based on accumulation processes alone. Clearly, this may have important clinical ramifications; if clinical outcomes are related to drug exposure, then a simple percentage increase in dose will have a much greater impact on total drug exposure than would be expected with a behavior based on linear pharmacokinetics. Trough plasma concentrations drawn around day 14 to 16 do not show trends suggesting that steady-state was reached. Most importantly, at the recommended dose for further clinical studies applying continuous dosing regimens with SCH 66336, trough plasma concentrations were shown to exceed 1.5 $\mu\text{mol/L}$, which is above concentrations required in vitro to induce significant growth inhibition in

colony assays against various primary human tumor specimens.²⁸

The general principles of dose dependency in pharmacokinetics have recently been reviewed.²⁹ The dose-dependent pharmacokinetic behavior of SCH 66336 in cancer patients most likely involves multiple nonlinear (absorption) mechanisms, including saturation of metabolic processes responsible for presystemic biotransformation (eg, the cytochrome P450 system) or saturation of outward-directed drug-carrier systems that mediate transmembrane drug flux, such as *MDR1* P-glycoprotein. Saturation of presystemic metabolism or degradation in the gut lumen, the intestinal mucosae, or the liver after oral administration of drugs in humans is relatively common and has been well described for the calcium antagonist verapamil³⁰ and also for fluorouracil.³¹ However, the phenomenon of a dose-dependent decrease in extravascular binding ($V_{d,ss}/F$) as seen here with SCH 66336 is highly unusual, although it has been reported to occur with 3-hour infusions of paclitaxel, presumably as a result of extensive binding to microtubules or micellar encapsulation in its formulation vehicle.³² Further analysis of the absorption and disposition of SCH 66336 in individual cancer patients, with respect to the current findings, should be of great importance for our ability to better understand the role of the various biologic factors that may influence the compound's pharmacokinetic behavior and pharmacologic actions, and effects of other drug administered concomitantly.

In conclusion, this phase I and pharmacologic study with continuous oral bid SCH 66336 has shown that this farnesyl transferase inhibitor can be safely administered using a continuous oral bid dosing schedule. The recommended dose for phase II studies using this treatment schedule is 200 mg bid.

REFERENCES

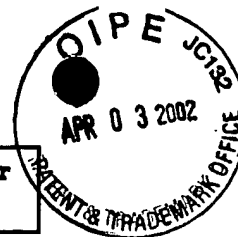
1. Gibbs JB: Ras C-terminal processing enzymes: New drug targets? *Cell* 65:1-4, 1991
2. Lowy DR, Willumsen BM: Function and regulation of Ras. *Annu Rev Biochem* 62:851-891, 1993
3. Khosravi-Far R, Der CJ: The Ras signal transduction pathway. *Cancer Metastasis Rev* 13:67-89, 1994
4. Gibbs JB, Ollif A, Kohl NE: Farnesyltransferase inhibitors: Ras research yields a potential cancer therapeutic. *Cell* 77:175-178, 1994
5. Gibbs JB, Kohl NE, Koblan KS, et al: Farnesyltransferase inhibitors and anti Ras therapy. *Breast Cancer Res Treat* 38:75-83, 1996
6. Omer CA, Kohl NE: $\text{CA}_1\text{A}_2\text{X}$ -competitive inhibitors of farnesyltransferase as anti-cancer agents. *Trends Pharmacol Sci* 18:437-444, 1997
7. Gibbs JB, Ollif A: The potential of farnesyltransferase inhibitors as cancer chemotherapeutics. *Annu Rev Pharmacol Toxicol* 37:143-166, 1997
8. Rowinsky EK, Windle JJ, Von Hoff DD: Ras protein farnesyl transferase: A strategic target for anticancer therapeutic development. *J Clin Oncol* 17:3631-3652, 1999
9. Ollif A: Farnesyl transferase inhibitors: Targeting the molecular basis of cancer. *Biochim Biophys Acta* 1423:C19-C30, 1999
10. Bos JL: *ras* oncogenes in human cancer: A review. *Cancer Res* 49:4682-4689, 1989
11. Prendergast JC: Targeting farnesyltransferase: Is *Ras* relevant? *ASCO Educational Book* Spring:22-28, 1999
12. Liu M, Lee S, Yaremko B, et al: SCH 66336, an orally bioavailable tricyclic farnesyl protein transferase inhibitor, demonstrates broad and potent in-vivo antitumor activity. *Proc Am Assoc Cancer Res* 39:270, 1998 (abstr 1843)
13. Izbicka E, Lawrence R, Davidson K, et al: Activity of a farnesyl transferase inhibitor (SCH 66336) against a broad range of tumors taken directly from patients. *Proc Am Assoc Cancer Res* 40:524, 1999 (abstr 3454)

14. Liu M, Bryant MS, Chen J, et al: Antitumor activity of SCH 66336, an orally bioavailable tricyclic inhibitor of farnesyl protein transferase in human tumor xenograft models and *wap-ras* transgenic mice. *Cancer Res* 58:4947-4956, 1998
15. World Health Organization: WHO handbook for reporting results of cancer treatment. Geneva, Switzerland, World Health Organization, 1979 (Offset Publication No. 40)
16. Kim H, Likhari P, Lin CC, et al: High-performance liquid chromatographic analysis of the antitumor agent SCH 66336 in cynomolgus monkey plasma and evaluation of its chiral inversion in animals. *J Chromatogr B Biomed Sci Appl* 728:133-141, 1999
17. Gibaldi M, Perrier D: Noncompartmental analysis based on statistical moment theory, in *Pharmacokinetics* (ed 2). New York, NY, and Basel, Switzerland, Marcel Dekker, 1982, pp 409-417
18. Adjei AA, Erlichman Ch, Davis JN, et al: A phase I trial of the farnesyl protein transferase (FPT) inhibitor SCH 66336: Evidence for biological and clinical activity. *Cancer Res* 60:1871-1877, 2000
19. Hurwitz HI, Colvin OM, Petros WP, et al: Phase I and pharmacokinetic study of SCH 66336, a novel FPTI, using a 2-week on, 2-week off schedule. *Proc Am Soc Clin Oncol* 18:156a, 1999 (abstr 599)
20. Awada A, Eskens FALM, Piccart MJ, et al: A clinical, pharmacodynamic and pharmacokinetic phase I study of SCH 66336 (SCH), an oral inhibitor of the enzyme farnesyl transferase, given once daily in patients with solid tumors. *Clin Cancer Res* 5:3733s, 1999 (suppl, abstr 20)
21. Britten CD, Rowinsky E, Yao S-L, et al: The farnesyl protein transferase (FPTase) inhibitor L-778,123 in patients with solid cancers. *Proc Am Soc Clin Oncol* 18:155a, 1999 (abstr 597)
22. Rubin E, Abbruzzese JL, Morrison BW, et al: Phase I trial of the farnesyl protein transferase inhibitor L-778,123 on a 14 or 28-day schedule. *Proc Am Soc Clin Oncol* 19:178a, 2000 (abstr 689)
23. Schellens J, De Klerk G, Swart M, et al: Phase I and pharmacologic study with the novel farnesyl transferase inhibitor (FTI) R115777. *Proc Am Soc Clin Oncol* 19:184a, 2000 (abstr 715)
24. Hudes G, Schol J, Baab A, et al: Phase I clinical and pharmacokinetic trial of the farnesyl transferase inhibitor R115777 on a 21-day dosing schedule. *Proc Am Soc Clin Oncol* 18:156a 1999 (abstr 601)
25. Zujewski J, Horak ID, Bol CJ, et al: Phase I and pharmacokinetic study of farnesyl transferase inhibitor R115777 in advanced cancer. *J Clin Oncol* 18:927-941, 2000
26. Ryan DP, Eder JP, Supko JG, et al: Phase I clinical trial of the farnesyltransferase (FT) inhibitor BMS-214662 in patients with advanced solid tumors. *Proc Am Soc Clin Oncol* 19:185a, 2000 (abstr 720)
27. Bryant MS, Liu M, Wang S, et al: Pharmacokinetics of a potent orally bioavailable inhibitor of farnesyl protein transferase in the mouse, rat and cynomolgus monkey. *Proc Am Assoc Cancer Res* 39:177, 1998 (abstr)
28. Petit T, Izbicka E, Lawrence RA, et al: Activity of SCH 66336, a tricyclic farnesyltransferase inhibitor, against human tumor colony-forming units. *Ann Oncol* 10:449-453, 1999
29. Lin JH: Dose-dependent pharmacokinetics: Experimental observations and theoretical considerations. *Biopharm Drug Dispos* 15:1-31, 1994
30. Freedman SB, Richmond DR, Ashley JJ, et al: Verapamil kinetics in normal subjects and patients with coronary artery spasm. *Clin Pharmacol Ther* 30:644-652, 1981
31. Wagner JG, Gyves JW, Stetson CL, et al: Steady-state nonlinear pharmacokinetics of 5-fluorouracil during hepatic arterial and intravenous infusions in cancer patients. *Cancer Res* 46:1499-1506, 1986
32. Kearns CM, Gianni L, Egorin MJ: Paclitaxel pharmacokinetics and pharmacodynamics. *Semin Oncol* 22:16-23, 1995 (suppl 6)



get the journal delivered to your
 mailbox!

HOME HELP FEEDBACK SUBSCRIPTIONS ARCHIVE SEARCH SEARCH RESULT



RECEIVED

APR 05 2002

TECH CENTER 1600/2900

The Oncologist, Vol. 5, No. 2, 99-107, April 2000
 © 2000 AlphaMed Press

Oral Chemotherapeutic Agents for Colorectal Cancer

Sunil Sharma^a, Leonard B. Saltz^{a,b}

^a Gastrointestinal Oncology Service, Division of Solid Tumor Oncology, Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, New York, USA;

^b Department of Medicine, Weil Medical College, Cornell University, New York, New York, USA

Correspondence: Sunil Sharma, M.D., Gastrointestinal Oncology Service, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, New York 11201, USA. Telephone: 212-639-8702; Fax: 212-717-3320; e-mail: sharma1@mskcc.org

► Abstract

A number of novel oral chemotherapeutic agents are entering practice or are under development in the United States. Many of these agents display significant clinical activity against colorectal cancer. Many classes of compounds, including fluoropyrimidine analogs, dihydropyrimidine dehydrogenase (DPD) inhibitors, topoisomerase inhibitors, farnesyl transferase inhibitors, and others, are being developed for oral administration. This manuscript describes the progress of clinical development of these agents and also explores the relative merits and challenges of these approaches. Economic issues, patient preference, and patient selection issues surrounding oral chemotherapy for colorectal cancer will also be discussed.

Key Words: Oral chemotherapy · Colon cancer · Rectal cancer · Economic analysis · Patient compliance

► Introduction

Colorectal cancer is the second most common cause of cancer mortality in the United States. It has been estimated that 129,400 new cases will be diagnosed in 1999 [1]. Colorectal cancer can be cured in the early stages and in selected patients with advanced

- [Abstract of this Article](#)
- [Reprint \(PDF\) Version of this Article](#)
- [Similar articles found in:](#)
 [The Oncologist Online](#)
 [PubMed](#)
- [PubMed Citation](#)
- [This Article has been cited by:](#)
 [other online articles](#)
- [Search Medline for articles by:](#)
 [Sharma, S. || Saltz, L. B.](#)
- [Download to Citation Manager](#)

- ▲ [Top](#)
- [Abstract](#)
- ▼ [Introduction](#)
- ▼ [Rationale for Oral Chemotherapy...](#)
- ▼ [Novel Fluoropyrimidines and...](#)
- ▼ [Challenges in Development of...](#)
- ▼ [Combination Chemotherapy with...](#)
- ▼ [Economic Considerations for...](#)
- ▼ [Patient Preferences for Oral...](#)
- ▼ [Conclusions](#)
- ▼ [References](#)

- ▲ [Top](#)
- ▲ [Abstract](#)
- [Introduction](#)
- ▼ [Rationale for Oral Chemotherapy...](#)
- ▼ [Novel Fluoropyrimidines and...](#)
- ▼ [Challenges in Development of...](#)

disease by definitive resection, however, chemotherapy for advanced and metastatic disease remains disappointing. Treatment of metastatic colorectal cancer with chemotherapy is a palliative approach. Complete responses to front-line chemotherapy are rarely observed, and partial responses are observed in less than 25% of patients [2]. With the recent introductions of irinotecan and oxaliplatin, there has been an extension of the repertoire available to the clinician. However, all of these agents can have significant toxicity (gastrointestinal toxicity, myelosuppression, and neurotoxicity) and require repeated clinical visits and/or infusion pumps for administration on a long-term basis.

- ▼ [Combination Chemotherapy with...](#)
- ▼ [Economic Considerations for...](#)
- ▼ [Patient Preferences for Oral...](#)
- ▼ [Conclusions](#)
- ▼ [References](#)

► Rationale for Oral Chemotherapy in Colorectal Cancer

There has been interest in development of oral chemotherapy agents for cancer therapeutics for a long period of time, beginning with the development of agents such as busulfan and hydroxyurea. Administration of oral chemotherapy has several potential advantages. These include the potential for greater patient convenience and acceptance and significant cost savings, both in terms of treatment costs and lost wages incurred by patients and family during physician visits [3]. There is evidence that with regular patient education and monitoring, adequate patient compliance to oral medications can be achieved, although issues of compliance and safety remain a concern [4]. Recently, there has been a surge in the development of oral therapies for colorectal cancer. We present an overview of several such drugs in various stages of clinical development.

- ▲ [Top](#)
- ▲ [Abstract](#)
- ▲ [Introduction](#)
- [Rationale for Oral Chemotherapy...](#)
- ▼ [Novel Fluoropyrimidines and...](#)
- ▼ [Challenges in Development of...](#)
- ▼ [Combination Chemotherapy with...](#)
- ▼ [Economic Considerations for...](#)
- ▼ [Patient Preferences for Oral...](#)
- ▼ [Conclusions](#)
- ▼ [References](#)

► Novel Fluoropyrimidines and Dihydropyrimidine Dehydrogenase (DPD) Inhibitors

Fluoropyrimidines, for example, 5-fluorouracil (5-FU) and fluorodeoxyuridine (FUDR), have been successfully used in the treatment of colorectal cancer for more than four decades. Currently, there are several oral fluoropyrimidines in clinical practice or in advanced stages of development.

Capecitabine

Capecitabine (XelodaTM, Roche Pharmaceuticals; Nutley, NJ) is an oral fluoropyrimidine that is now commercially available. It is a prodrug of 5-FU and is absorbed intact from the intestine. It is converted to doxifluridine by the sequential action of acylamidase isoenzyme A and cytidine deaminase in the liver. The latter enzyme is also present in tumor tissue. Doxifluridine, in turn, is converted to 5-FU in normal and tumor tissue by thymidine phosphorylase (TP) [5], and levels of TP are higher in some tumor tissues than in normal

- ▲ [Top](#)
- ▲ [Abstract](#)
- ▲ [Introduction](#)
- ▲ [Rationale for Oral Chemotherapy...](#)
- [Novel Fluoropyrimidines and...](#)
- ▼ [Challenges in Development of...](#)
- ▼ [Combination Chemotherapy with...](#)
- ▼ [Economic Considerations for...](#)
- ▼ [Patient Preferences for Oral...](#)
- ▼ [Conclusions](#)
- ▼ [References](#)

tissues. In some human tumor xenograft models, capecitabine seemed to be more effective as compared to 5-FU [6]. Antitumor activity was reported in a fluorouracil-resistant xenograft model [7]. There seemed to be a higher degree of 5-FU in the tumor as compared to healthy tissue after capecitabine administration to colorectal cancer patients [8]. This may also be due to higher levels of TP present in tumor tissues [9]. Major toxicities in phase I trials have included diarrhea, palmar-plantar erythrodysesthesia (hand-foot syndrome), nausea, vomiting, dizziness, and stomatitis [10, 11]. Myelosuppression was not seen in these phase I trials to any appreciable degree. In pharmacokinetic studies, capecitabine displayed linear pharmacokinetics with good gastrointestinal absorption [12]. Recently, preliminary results of a three-arm, randomized phase II trial of capecitabine on continuous and intermittent schedules and, as a third arm, in combination with leucovorin were reported [13]. The study demonstrated comparable efficacy in all arms with several complete responses. Moderate toxicity was observed in all arms, with hand-foot syndrome, stomatitis, and diarrhea being the most commonly observed toxicities. Based on these studies, the intermittent schedule (14 of 21 days) without leucovorin was taken into phase III trials. The recommended phase II dose of 2,500 mg/m²/day in twice-a-day divided doses, for two of three weeks has been developed for therapeutic use. In the European phase III trial [14], 602 untreated colorectal patients with metastatic disease were randomized to receive either capecitabine or 5-FU/leucovorin on the daily x 5 (one tablet a day for five consecutive days) Mayo regimen. There was a higher response rate in the capecitabine arm (26.6% versus 17.9%, $p = .013$), although the response duration and progression-free survival were comparable in both arms. In addition, the complete response (CR) rate was also similar in both arms (2.3%). While hand-foot syndrome and diarrhea were more common with capecitabine, neutropenia and its attendant complications were more common in the 5-FU/leucovorin control arm. In the United States, phase III trial [15], 605 patients were randomized to the identical arms as above. Again, the response rates were higher in the capecitabine arm (23.2% versus 15.5%, $p = .02$) but this did not translate into higher CR rates, duration of response, or progression-free survival. Similar toxicity data were obtained as in the European trial. Capecitabine has been approved for treatment of metastatic breast cancer by the Food and Drug Administration, and combination trials of capecitabine are planned. It seems from the above data that use of capecitabine as a single agent in the first-line treatment of colorectal cancer could be a consideration, although the final word will have to be postponed until broader experience has been obtained and peer review publications are examined.

UFT

UFT (OrzelTM, Bristol Myers Squibb; Princeton, NJ) is a combination of tegafur, a prodrug of 5-FU, and uracil in a molar ratio of 1:4. Tegafur is converted to 5-FU by hepatic cytochrome P450 pathway [16], whereas uracil enhances the half-life of converted 5-FU by competing for its degradation by DPD, which is the rate-limiting enzyme in the catabolism of 5-FU. This leads to higher intracellular concentrations of 5-FU with increased antitumor activity in preclinical models [17] and in tumor tissues when given to humans [18].

Tegafur has been approved for clinical use in Japan, and it had a response rate of 10% in advanced gastrointestinal malignancies [19]. Clinical utility of tegafur has been limited because of the neurologic toxicity observed. This can manifest as depression, anosmia, headache, and dizziness. This neurotoxicity

is due to an inactive metabolite generated during conversion of tegafur to 5-FU. Since uracil greatly reduces the amount of tegafur used, the amount of this metabolite becomes negligible.

Phase I trials of UFT were initially conducted in Japan and subsequently in the United States. In the United States trials, UFT was evaluated most commonly as a three times daily dose given for 5 of 21 or 28 of 35 to 42 days [20-22]. The most common toxicities were myelosuppression on the five-day schedule and diarrhea on the 28-day schedule. No neurotoxicity was observed. When administered on a 28-day schedule, plasma concentrations of 5-FU were comparable to those achieved with continuous intravenous administration. No neurotoxicity was seen.

Because of enhancement of antitumor activity of 5-FU with simultaneous administration of leucovorin and similar enhancement of UFT activity in animal models [23], UFT was next evaluated in combination with oral leucovorin in phase I trials. In two trials using the 28-day UFT regimen, diarrhea was dose limiting. Several phase II trials of UFT have now been reported in colorectal cancer and are summarized in Table 1. As seen from the table, UFT was well tolerated in combination with calcium folinate, and toxicity was proportional to administered dose. In addition, there was evidence of moderate activity in each of these schedules [24]. Based on these trials, a combination of 300 mg/day of UFT with 75-90 mg/day of leucovorin was selected for further clinical development. Results of two phase III trials have now been reported for the UFT/oral leucovorin combination. In the first study [25], 816 patients were randomized between Orzel (UFT at 300 mg/m²/day with 75-90 mg/day of leucovorin) and intravenous 5-FU and leucovorin arms (5-FU 425 mg/m²/day and leucovorin 20 mg/m²/day for five days every 28 days). The overall response rates in both arms were comparable (12% for UFT/leucovorin and 15% for intravenous 5-FU and leucovorin). The UFT/leucovorin arm had reduced incidence of febrile neutropenia and hand-foot syndrome. UFT-leucovorin combinations are also being explored for development in adjuvant therapy of colon and rectal cancer [26-29]. The National Surgical Adjuvant Breast and Bowel Project (NSABP) has conducted a randomized phase III trial in resected stage II and III colon cancer between 5-FU/leucovorin and UFT/leucovorin (NSABP C-06). This trial is now closed to accrual. A postoperative oral UFT/leucovorin and radiotherapy trial is currently open for rectal cancer at Memorial Sloan-Kettering Cancer Center and a preoperative trial in the same disease is ongoing at M.D. Anderson Cancer Center [27].

View this table: Table 1. Representative phase II trials of UFT in colorectal carcinoma

[\[in this window\]](#)

[\[in a new window\]](#)

S-1

S-1 (Taiho Pharmaceutical Ltd.; Tokyo, Japan) combines tegafur, 5-chloro-2,4-dihydropyridine (CDHP), and oxonic acid in a molar ratio of 1:0.4:1. CDHP inhibits activity of DPD and oxonic acid prevents intestinal phosphorylation of 5-FU by pyrimidine-phosphoribosyl-transferase. The development of S-1 in colorectal cancer is primarily being pursued at this time by the European Organisation for Research and Treatment of Cancer (EORTC) Early Clinical Studies Group (ECSCG). In

their first reported experience [30], 36 patients were treated with S-1 at a dose of 35 mg/m² twice daily after meals (the first four patients at a dose of 40 mg/m² twice daily had gastrointestinal toxicity). The most common side effects at this dose were diarrhea, nausea, fatigue, and anorexia. Four patients had a partial response and further development work is underway.

Eniluracil (5-Ethynyluracil)

Eniluracil (Glaxo Wellcome; Research Triangle Park, NC; 776C85, GW776) is an extremely potent noncompetitive inhibitor of DPD. Eniluracil is not a prodrug of 5-FU or an anticancer agent, rather, it potentiates the effects of 5-FU by causing virtually complete inhibition of DPD. Since DPD is the major inactivator of 5-FU, eniluracil greatly increases the bioavailability of 5-FU in animal models [31]. In a single-agent study, eniluracil was administered at a dose of 10 mg/m² twice daily for three days prior to surgery [32]. In tumor samples collected at surgery, there was complete suppression of the tumor DPD catalytic activity. There was also complete suppression of systemic DPD activity in mononuclear cells. Since erratic bioavailability of oral 5-FU is thought to be a reflection of intestinal and hepatic DPD activity [33], a combination of oral 5-FU and eniluracil has been developed. In the phase I trial [34], eniluracil therapy caused a sustained decrease in DPD activity by at least 90% in mononuclear cells for 24 h or longer. The recommended phase II doses for combination of eniluracil and oral 5-FU in the study were 50 mg/day and 15 mg/m²/day, respectively, when given on a daily x 5 schedule every four weeks. The major toxicities in this study were myelosuppression, diarrhea, and mucositis. However, small increases in the doses of oral 5-FU above the acceptable dose level led to substantial increases in the incidence of toxicities in this study. In the pharmacokinetic analysis, complete bioavailability (100%) of 5-FU with a half-life of 4.5 h was observed, and interpatient variability was reduced as compared to intravenous 5-FU administration [35]. In addition, a strong correlation between 5-FU clearance, calculated creatinine clearance, and serum creatinine levels was observed. Thus, eniluracil should be used with extreme caution in patients with renal dysfunction.

In a recently reported phase II trial, eniluracil in combination with oral 5-FU was administered on a twice daily schedule for 28 days of a five-week course [36]. In untreated patients with metastatic colorectal cancer this regimen had a 24% response rate. Diarrhea (13%), stomatitis (3%), and myelosuppression (3%) were the major dose-limiting toxicities. This combination has also been tested with oral leucovorin [37]. A similar response rate (33%) was observed in this trial. The Eastern Cooperative Oncology Group (ECOG) has initiated a randomized phase III trial comparing a combination of oral 5-FU and eniluracil versus continuous infusion 5-FU in patients with advanced colorectal cancer.

Other Agents

Other agents, including BOF-A2 (Emetifur), which combines 1-ethoxymethyl 5-fluorouracil (EM-FU), which is a slow-release form of 5-FU with 3-cyano-2,6,-dihydropyrimidine (CNDP), which inhibits DPD, are also in development [38].

Topoisomerase I Inhibitors

Topoisomerase I (topo-I) is an enzyme used by dividing cells to relax DNA supercoiling. Camptothecins are a class of recently characterized compounds that stabilize the DNA-topoisomerase I cleavable

complex, thereby inhibiting the normal repair of the nicks introduced by topo-I. This, in turn, leads to more lethal DNA damage in the presence of high rates of ongoing DNA synthesis [39]. Irinotecan (CPT-11) is a highly active topo-I inhibitor and is approved for treatment of metastatic colorectal cancer in the United States by parenteral administration. Several newer camptothecin analogs and an oral formulation of CPT-11 are under development.

Irinotecan

Irinotecan (CampostarTM, Pharmacia & Upjohn; Kalamazoo, MI), administered intravenously, has demonstrated considerable clinical activity in colorectal cancer. In animal models, protracted oral administration of camptothecins had superior tumor response rates compared to intermittent intravenous treatment and also demonstrated reduced toxicity [40]. Also, liver has high levels of carboxylesterase, the enzyme that converts CPT-11 to its active form, SN-38. Since oral agents are preferentially taken up by the portal circulation, oral administration could lead to more efficient activation of CPT-11 to SN-38. Thus, theoretically, this could be advantageous for treatment of liver metastases from colon cancer. In a phase I trial of intravenous formulation of irinotecan administered in fruit juice orally, the toxicity profile was similar to intravenous administration. Cholinergic symptoms were less commonly observed and there was evidence of antitumor activity in metastatic colorectal cancer [41]. Delayed diarrhea was the major toxicity and myelosuppression was seen at higher dose levels. Equivalent biological activity, when compared to the intravenous dosing, was observed at tolerable dose levels even with substantially lower areas under the curve for CPT-11 lactone. A new powder-filled capsular formulation of irinotecan is in phase I trials in the United States and Europe on two different schedules: a 5 of 21-day schedule in Europe and a 14 of 21-day schedule at Memorial Sloan-Kettering Cancer Center. An additional five-day administration schedule is being developed at the Mayo Clinic. Future combination trials with oral fluoropyrimidines are also planned.

9-Aminocamptothecin

A colloidal dispersion formulation of 9-aminocamptothecin (9-AC) was tested in phase I trials recently. Marked interpatient variability was reported with poor correlation to the dose administered [42]. In another trial, using a different formulation, rapid drug absorption and bioavailability in the range of 27% to 49% were observed [43]. In several different intravenous schedules, 9-AC was found to lack activity in metastatic colorectal cancer [43-46]. The oral formulation may be developed for further study after the initial evaluation is completed. Given the lack of activity of this agent in the parenteral form in colorectal cancer, however, it is unlikely that this agent will play a major role in this disease.

9-Nitrocamptothecin

Since 9-nitrocamptothecin (9-NC) has broad antitumor activity in animal models, it has been evaluated as an oral formulation in adult cancers. A maximum tolerated dose of 1.5 mg/m²/day on a five-consecutive-day, every-week schedule was observed [47]. Significant toxicities were observed, notably nausea, neutropenia, thrombocytopenia, and cystitis. Several antitumor responses were observed, and phase II trials in colon cancer are ongoing.

Farnesyltransferase Inhibitors

Ras proteins are normally associated with the inner surface of plasma membrane and act as

intermediates in transmitting a wide variety of extracellular signals to the cytoplasm and the nucleus. *Ras* oncogenes are mutated in more than 40% of colonic adenocarcinomas and mutation leads to constitutive activation of *ras* [48]. Association of *ras* with the inner surface of plasma membrane is facilitated by farnesyl protein transferase (FPT), which modifies the cysteine residues on the protein. A variety of farnesyl transferase inhibitors is in clinical development and a selection of these oral agents are discussed below.

SCH66336

SCH66336 (Schering-Plough Research; Kenilworth, NJ) is a nonpeptidic small molecule with a tricyclic nucleus and is a potent and selective inhibitor of FPT. In preclinical studies, this compound inhibits growth of cell lines expressing mutated *K-ras*. In vivo studies have demonstrated that SCH66336 has potent antitumor activity against colon xenografts among many other types of implanted tumors in nude mice [49]. In two phase I trials [50, 51], SCH66336 was given orally twice daily as continuous administration or on a two of four-week schedule. The recommended phase II dose in both trials was 200 mg twice a day. The primary toxicities were diarrhea, anorexia, fatigue, and nausea. These toxicities were described as being mild and reversible on discontinuation of therapy. In the intermittent administration trial, two patients with colon cancer exhibited stable disease for four months. Recently, a continuous once-daily dosing trial was also reported [52]. An equivalent dose of SCH66336 (400 mg/day) was well tolerated on this schedule. Phase II trials are ongoing with SCH66336 as a single agent in chemotherapy-resistant colorectal cancers, and phase I trials in combination with 5-FU are in progress.

R115777

R115777 (Janssen Research Foundation; Titusville, NJ) is an oral quinolone analog that inhibits farnesylation with consequent inhibition of growth of a variety of human tumor cell lines at nanomolar concentrations [53]. In human tumor xenografts of colon cancer, R115777 inhibited tumor growth without any overt toxicity [53]. Two phase I trials have been reported with this compound. In the first trial [54], R115777 was administered orally twice a day for 21 of 28 days. The recommended phase II dose on this schedule was 240 mg/m² as a twice daily dose. The principal toxicities were myelosuppression (neutropenia and thrombocytopenia), fatigue, and confusion. Plasma levels at the well-tolerated dose were equivalent to concentrations required for in vitro activity. In the second trial, R115777 was administered twice daily for five days every two weeks [55]. This regimen was not very myelosuppressive, but nausea, vomiting, headache, fatigue, and neuropathy were observed. A phase I trial combining chronic daily administration of R115777 along with bimonthly 5-FU and leucovorin administration has also been reported in patients with colorectal or pancreatic cancer [56]. Myelosuppression was the principal toxicity and final results are awaited regarding a recommended phase II dose in these patients.

Challenges in Development of Oral Chemotherapy for Colorectal Cancer

There are several challenges facing the development of oral

▲ [Top](#)

chemotherapy for colorectal cancer. In phase I and II trials of oral chemotherapy, our experience has been that patients have needed considerable supervision at home. This means that patients enrolled in these trials (not unlike other trial candidates) need to have a high degree of motivation and reliability. Patients have self-modulated drug dosages in our experience. In clinical trials, a requirement has been that meticulous records be kept by the patient and regular reviews of these records along with other drug audits (including pill counting and intermittent telephone verifications) be carried out by the research staff. Often, research nurses make regular phone calls to patients to inquire about compliance and toxicity, or to make recommendations regarding continuing or delaying toxicity. Sponsors have been generally willing to bear the higher costs associated with this intense monitoring and follow-up of patients enrolled in these trials. There are several unresolved questions regarding issues of administration of these drugs in the community setting. It may not be possible to monitor patients as closely as in standard practice. It may then be difficult to observe similar safety profiles seen in the research studies. Optimal follow-up strategies including patient visits, hematologic monitoring, etc., have not been defined for "real world" settings and may have to await larger trials and, possibly, postmarketing data collection. No published data have evaluated postmarketing "real-life" compliance issues surrounding the administration of oral chemotherapy with agents like capecitabine and UFT, although this would be of great interest.

- ▲ [Abstract](#)
- ▲ [Introduction](#)
- ▲ [Rationale for Oral Chemotherapy...](#)
- ▲ [Novel Fluoropyrimidines and...](#)
- [Challenges in Development of...](#)
- ▼ [Combination Chemotherapy with...](#)
- ▼ [Economic Considerations for...](#)
- ▼ [Patient Preferences for Oral...](#)
- ▼ [Conclusions](#)
- ▼ [References](#)

A major issue in development of the oral chemotherapy is a strict evaluation of concomitant medications. For instance, 18 Japanese patients were reported to have died because of coadministration of tegafur with sorivudine, a new antiviral therapy for herpes zoster. The mechanism of action appears to be DPD inhibition by a metabolite of sorivudine [57]. Other drugs, for example, antacids, salicylates, antibiotics, anticonvulsants, etc., can sometimes have significant interactions associated with oral chemotherapy. Some of these agents administered orally can interfere with the absorption and also compete for the first-pass elimination of chemotherapy from the hepatic parenchyma. In one report, for example, acute phenytoin intoxication was observed in patients on tegafur, presumably because of interference of phenytoin metabolism by tegafur [58]. Some of these medications may lead to large inter- and inpatient variability in toxicity and efficacy, depending on concomitant medications being taken by the patients.

► Combination Chemotherapy with Oral Agents

Combination therapies with oral agents utilize similar rationales as traditional combination chemotherapy trials. Primarily, there is hope of synergy with nonoverlapping toxicities when two or more agents are combined. Preliminary results from some trials combining parenteral 5-FU and irinotecan [59, 60] or oxaliplatin and 5-FU [61] seem promising, with higher overall response rates

- ▲ [Top](#)
- ▲ [Abstract](#)
- ▲ [Introduction](#)
- ▲ [Rationale for Oral Chemotherapy...](#)
- ▲ [Novel Fluoropyrimidines and...](#)
- ▲ [Challenges in Development of...](#)
- [Combination Chemotherapy with...](#)
- ▼ [Economic Considerations for...](#)
- ▼ [Patient Preferences for Oral...](#)

in metastatic disease and suggestive trends toward improved survival.

▼ [Conclusions](#)
▼ [References](#)

Combination therapies with oral agents are in the planning stages and will generate new challenges. These will involve issues of scheduling two or more oral drugs, and the potential for complex pharmacokinetic interactions. The various combinations that are of interest include intravenous irinotecan and oral fluoropyrimidines, oral irinotecan and oral fluoropyrimidines, oxaliplatin and oral fluoropyrimidines, oxaliplatin and oral irinotecan, etc. In addition, there are ongoing trials to evaluate oral chemotherapy agents with radiation in rectal carcinoma. Preliminary results from Europe are promising for neoadjuvant treatment with UFT/folinic acid in rectal cancer [62]. Other agents will likely be evaluated with radiation in the future. Further information about open clinical trials can be obtained from the National Cancer Institute website: <http://cancernet.nci.nih.gov/trialsrch.shtml>

► Economic Considerations for Development of Oral Chemotherapy

Intravenous chemotherapy for colon cancer can be expensive. In a study comparing the relative costs of bolus and infusional 5-FU for colon cancer therapy, the average cost of administration was related to length of infusion and bolus schedule [63]. In this retrospective analysis done in 1996, the authors estimated that infusion schedules of 28-day and five-day durations incurred an average cost of \$2,360 and \$1,338 per month, respectively. On the other hand, the five-day or weekly bolus schedules incurred a cost of \$1,250 or \$2,081, respectively. This analysis incorporated cost of doctor visits, laboratory monitoring, and pharmacy costs. The actual cost of administering this chemotherapy is, in reality, higher when other considerations, for example, time lost at work for visits and hospitalizations, are taken into account [64].

▲ [Top](#)
▲ [Abstract](#)
▲ [Introduction](#)
▲ [Rationale for Oral Chemotherapy...](#)
▲ [Novel Fluoropyrimidines and...](#)
▲ [Challenges in Development of...](#)
▲ [Combination Chemotherapy with...](#)
• [Economic Considerations for...](#)
▼ [Patient Preferences for Oral...](#)
▼ [Conclusions](#)
▼ [References](#)

Oral chemotherapy has been widely thought to have a potential for cost savings when compared to intravenous chemotherapy. However, cost of chemotherapy is dependent on a variety of factors, including clinic visits, cost of laboratory tests, costs incurred due to loss of productivity, etc. The Red Book estimates the average wholesale price for chemotherapy agents and is widely utilized by pharmacists. Table 2□ indicates the wholesale cost of some chemotherapy agents published in the Red Book in 1999. As can be seen from this analysis, newer oral chemotherapy may be more expensive than the older intravenous counterparts. There is no reason to believe that oral chemotherapy is less toxic and would require less close monitoring than intravenous chemotherapy. Thus, a monthly cost comparison of the cost of capecitabine as compared to 5-FU by a protracted 28-day infusion indicates equivalent charges generated by both regimens (Table 3□). Thus, although, oral chemotherapy has the potential of generating substantial savings in the long term, higher drug costs associated with newer and recently approved oral therapies may negate this potential in the initial years after drug approval. In the initial years after approval, there are also challenges facing providers and patients to convince insurance

companies and prescription plans to pay for the oral agents. This may be difficult if the newer agents are substantially more expensive and do not replicate research results in the community setting.

View this table: **Table 2. Representative costs of several oral and intravenous drugs in the United States**
[\[in this window\]](#)
[\[in a new window\]](#)

View this table: **Table 3. Comparative monthly cost of administering 5-fluorouracil (5-FU) as a 28-day infusion or capecitabine as oral therapy**
[\[in this window\]](#)
[\[in a new window\]](#)

► Patient Preferences for Oral Chemotherapy

In an elegant study by *Liu et al.* [65], 103 patients with cancer were questioned about their preference for oral or intravenous chemotherapy. Patients were told initially that clinic visits, laboratory evaluations, and toxicities of oral or intravenous regimens were comparable. Ninety-two of 103 patients expressed a preference for oral chemotherapy. The predominant reason for this appeared to be problems with intravenous access or convenience of administration outside a clinic setting.

Interestingly, most patients would not prefer oral chemotherapy if it was slightly inferior to intravenous chemotherapy. This study did not distinguish between patients receiving adjuvant or palliative chemotherapy or the performance status of patients participating in the study.

Practical experience has shown that many patients assume that oral chemotherapy is less toxic and "less serious." As more extensive experience is gained with oral chemotherapy, patient and physician perception may be altered. However, this will require ongoing education and will be a long-term process.

- ▲ [Top](#)
- ▲ [Abstract](#)
- ▲ [Introduction](#)
- ▲ [Rationale for Oral Chemotherapy...](#)
- ▲ [Novel Fluoropyrimidines and...](#)
- ▲ [Challenges in Development of...](#)
- ▲ [Combination Chemotherapy with...](#)
- ▲ [Economic Considerations for...](#)
- [Patient Preferences for Oral...](#)
- ▼ [Conclusions](#)
- ▼ [References](#)

► Conclusions

Oral chemotherapy is in a stage of rapid development for treatment of colorectal cancer. Various new oral agents are in advanced stages of development for treatment of these cancers around the world, but several challenges are being encountered by investigators in the development of these agents. In surveys, patients have expressed preference for these agents only if they

- ▲ [Top](#)
- ▲ [Abstract](#)
- ▲ [Introduction](#)
- ▲ [Rationale for Oral Chemotherapy...](#)
- ▲ [Novel Fluoropyrimidines and...](#)
- ▲ [Challenges in Development of...](#)
- ▲ [Combination Chemotherapy with...](#)
- ▲ [Economic Considerations for...](#)
- ▲ [Patient Preferences for Oral...](#)

are at least equivalent in efficacy to the traditional intravenous chemotherapy. Economic issues surrounding oral chemotherapy are complex and need to be evaluated prospectively in controlled trials. In the future, combination trials of these agents with each other, or with intravenous chemotherapy, are likely to advance the development and clarify a place for these compounds in the clinician's armamentarium.

- [Conclusions](#)
- ▼ [References](#)

► References

1. Landis SH, Murray T, Bolden S et al. Cancer statistics 1999. CA Cancer J Clin 1999;49:8-31.[Medline]
2. Cohen A, Minsky B, Schilsky P. Colorectal cancer. In: De Vita V, Hellman S, Rosenberg S, eds. Cancer: Principles and Practice of Oncology. Philadelphia: J.B. Lippincott, 1993:929-977.
3. DeMario MD, Ratain MJ. Oral chemotherapy: rationale and future directions. J Clin Oncol 1998;16:2557-2567.
[Abstract]
4. Lee CR, Nicholson PW, Souhami RL et al. Patient compliance with oral chemotherapy as assessed by a novel oral technique. J Clin Oncol 1992;10:1007-1013.[Abstract]
5. Ishitsuka H, Miwa M, Ishikawa T et al. Capecitabine: an orally available fluoropyrimidine with tumor selectivity. Proc Am Assoc Cancer Res 1995;36:2426a.
6. Ishikawa T, Sawada N, Sekiguchi F et al. Xeloda (capecitabine) a new oral fluoropyrimidine carbamate with an improved efficacy profile over other fluoropyrimidines. Proc Am Soc Clin Oncol 1997;16:796a.
7. Cao S, Lu K, Ishitsuka H et al. Antitumor efficacy of capecitabine against fluorouracil-sensitive and resistant tumors. Proc Am Soc Clin Oncol 1997;16:795a.
8. Schuller J, Reigner BG, Durston S et al. Tumor selectivity of Xeloda in colorectal cancer patients. Proc Am Soc Clin Oncol 1997;16:797a.
9. Takebayashi, Y, Yamada K, Maruyama I et al. The expression of thymidine phosphorylase and thrombomodulin in human colorectal carcinomas. Cancer Lett 1995;25:1-7
10. Meropol N, Budman D, Creaven P et al. A phase I study of continuous twice daily treatment with capecitabine in patients with advanced and/or metastatic tumors. Ann Oncol 1996;7(suppl 1):298a.
11. Hughes M, Planting A, Twelves C et al. A phase I study of intermittent twice daily oral therapy with capecitabine in patients with advanced and/or metastatic solid cancer. Ann Oncol 1996;7(suppl 1):297a.
12. Osterwalder B, Reigner B. Pharmacokinetics (PK) and pharmacodynamics (PD) of capecitabine in two phase I studies. Proc Am Soc Clin Oncol 1996;15:727a.
13. Findlay M, Van Custem E, Kocha W et al. A randomized phase II study of Xeloda (capecitabine) in patients with advanced colorectal cancer. Proc Am Soc Clin Oncol 1997;16:798a.
14. Twelves C, Harper P, Van Custem E et al. A phase III trial (S014796) of Xeloda in previously untreated advanced/ metastatic colorectal cancer. Proc Am Soc Clin Oncol 1999;18:1010a.
15. Cox JV, Pazdur R, Thibault A et al. A phase III trial of Xeloda in previously untreated advanced/metastatic colorectal cancer. Proc Am Soc Clin Oncol 1999;18:1016a.
16. El Sayed YM, Sadee W. Metabolic activation of ftorafur [R,S-1(tetrahydro-2-furanyl)-5-fluorouracil]: the microsomal oxidative pathway. Biochem Pharmacol 1982;31:3006-3008.

- ▲ [Top](#)
- ▲ [Abstract](#)
- ▲ [Introduction](#)
- ▲ [Rationale for Oral Chemotherapy...](#)
- ▲ [Novel Fluoropyrimidines and...](#)
- ▲ [Challenges in Development of...](#)
- ▲ [Combination Chemotherapy with...](#)
- ▲ [Economic Considerations for...](#)
- ▲ [Patient Preferences for Oral...](#)
- ▲ [Conclusions](#)
- [References](#)

[Medline]

17. Ohyama K, Koike D, Otake Y et al. Antineoplastic effect of UFT therapy (uracil-FT-207 combination therapy) on experimental pancreatic cancer transplanted in the pancreas and subcutaneous region. *Jpn J Cancer Chemother* 1982;9:2168-2174.
18. Fukui T, Imbayashi N, Nishi M et al. Clinical study on the enhancement of drug delivery into tumor tissue by using UFT. *Jpn J Cancer Chemother* 1980;7:2124-2129.
19. Futatsuki K, Komita T, Kamano T. Clinical results of treatment with the UFT fine granule preparation under cooperative study. Tokyo Cancer Chemotherapy Cooperative Study Group. *Jpn J Cancer Chemother* 1987;14:1274-1280.
20. Muggia F, Wu X, Spicer D et al. Phase I and pharmacokinetic study of oral UFT, a combination of the 5-fluorouracil prodrug tegafur and uracil. *Clin Cancer Res* 1996;2:1461-1467.[\[Abstract\]](#)
21. Pazdur R, Covington WP, Brown NS et al. Comparative steady state pharmacokinetics of oral UFT versus protracted intravenous 5-fluorouracil (FU). *Proc Am Soc Clin Oncol* 1996;474:1948a.
22. Pazdur R, Lassere Y, Diaz-Canton E et al. Phase I trials of uracil-tegafur (UFT) using 5 and 28 day administration schedules: demonstration of schedule dependent toxicities. *Anticancer Res* 1996;7:728-733.
23. Okabe H, Toko T, Saito H et al. Augmentation of the chemotherapeutic effectiveness of UFT, a combination of tegafur [1-(2-tetrahydrofuryl)-5-fluorouracil] with uracil, by oral l-leucovorin. *Anticancer Res* 1997;17:157-164.[\[Medline\]](#)
24. Pazdur R, Lassere Y, Rhodes V et al. Phase II trial of uracil and tegafur plus oral leucovorin: an effective oral regimen in the treatment of metastatic colorectal carcinoma. *J Clin Oncol* 1994;12:2296-2300.[\[Abstract\]](#)
25. Pazdur R, Douillard J-Y, Skillings JR et al. Multicenter phase III study of 5-fluorouracil (5-FU) or UFT in combination with leucovorin (LV) in patients with metastatic colorectal cancer. *Proc Am Soc Clin Oncol* 1999;18:1009a.
26. Mok TSK, Leung TWT, Chan ATC et al. A phase III randomized study of oral UFT (tegafur + uracil) as maintenance therapy in adjuvant treatment of surgically resected colorectal cancer patients. *Proc Am Soc Clin Oncol* 1998;17:1042a.
27. Hoff PM, Brito R, Slaughter M et al. Preoperative UFT, oral leucovorin (LV) and radiotherapy (RT) for patients with resectable rectal carcinoma: an oral regimen with complete pathologic responses. *Proc Am Soc Clin Oncol* 1998;17:860a.
28. Espinosa E, Gonzalez-Baron M, Feliu J et al. UFT-leucovorin as adjuvant treatment for Duke's B2-C colon cancer. *Proc Am Soc Clin Oncol* 1998;17:1059a.
29. Sadahiro S, Ohki S, Takahashi T et al. Pilot study on the new dose intensive oral UFT schedule as adjuvant chemotherapy for colorectal cancer. *Proc Am Soc Clin Oncol* 1998;17:1054a.
30. Schoffski P, Vermoken J, Schellens J et al. Safety, toxicity and antitumor efficacy of the modulated oral fluoropyrimidine derivative S-1 in patients with metastatic colorectal cancer: preliminary results of an early phase II study. *Clin Cancer Res* 1999;5(suppl):S3772.
31. Cao S, Rustum YM, Spector T. 5-Ethynyluracil (776C85): modulation of 5-fluorouracil efficacy and therapeutic index in rats bearing advanced colorectal carcinoma. *Cancer Res* 1994;54:1507-1510.[\[Abstract\]](#)
32. Ahmed FY, Johnston SJ, Cassidy J et al. Eniluracil treatment completely inactivates dihydropyrimidine dehydrogenase in colorectal cancers. *J Clin Oncol* 1999;17:2439-2445.
[\[Abstract/Full Text\]](#)
33. Spector T, Harrington JA, Porter DJ. 5-Ethynyluracil (776C85): inactivation of dihydropyrimidine dehydrogenase in vivo. *Biochem Pharmacol* 1993;46:2243-2248.[\[Medline\]](#)
34. Schilsky RL, Hohnaker J, Ratain MJ et al. Phase I and pharmacologic study of eniluracil plus fluorouracil in patients with advanced cancer. *J Clin Oncol* 1998;16:1450-1457.[\[Abstract\]](#)
35. Baker SD, Khor SP, Adjei AA. Pharmacokinetic, oral bioavailability, and safety study of fluorouracil in patients treated with 776C85, an inactivator of dihydropyrimidine dehydrogenase. *J Clin Oncol* 1996;14:3085-3096.[\[Abstract\]](#)

36. Mani S, Beck T, Chevlen E et al. A phase II open label study to evaluate a 28-day regimen of oral 5-fluorouracil (5-FU) plus 776C85 for the treatment of patients with previously untreated metastatic colorectal cancer (CRC). *Proc Am Soc Clin Oncol* 1998;18:1083a.
37. Schilsky R, Bukowski R, Burris H et al. A phase II study of 5-fluorouracil (5-FU) plus GW776 (776C85) with or without leucovorin in patients with metastatic colorectal cancer. *Proc Am Soc Clin Oncol* 1997;16:271a.
38. Matei S, Hoff PM, Brito R et al. Phase I trial of oral BOF-A2 plus leucovorin (LV) in advanced colorectal cancer: antitumor activity in fluorouracil-resistant patients. *Proc Am Soc Clin Oncol* 1998;18:882a
39. D'Arpa P, Beardmore C, Liu LF. Involvement of nucleic acid synthesis in cell killing mechanisms of topoisomerase poisons. *Cancer Res* 1990;50:6919-6924.[[Abstract](#)]
40. Houghton PJ, Clinton FS, Zamboni WC et al. Schedule dependent efficacy of camptothecins in models of human cancer. *Ann N Y Acad Sci* 1996;803:188-201.[[Medline](#)]
41. Drengler RA, Kuhn JG, Schaaf LJ et al. Phase I and pharmacokinetic trial of oral irinotecan administered daily for 5 days every 3 weeks in patients with solid tumors. *J Clin Oncol* 1999;17:685-696.[[Abstract/Full Text](#)]
42. Mani S, Iyer L, Janisch L et al. Phase I clinical and pharmacokinetic study of oral 9-aminocamptothecin (NSC-603071). *Cancer Chemother Pharmacol* 1998;42:84-87.[[Medline](#)]
43. Sparreboom A, Stoter G, Loos WJ et al. Oral bioavailability of 9-aminocamptothecin in adult patients with solid tumors. *Proc Am Assoc Cancer Res* 1997;38:504a.
44. Pazdur R, Medgysey DC, Winn RJ et al. Phase II trial of 9-aminocamptothecin administered as a 120-hr continuous infusion weekly for three weeks in metastatic colorectal cancer. *Invest New Drugs* 1998;16:341-346.[[Medline](#)]
45. Pazdur R, Diaz-Canton E, Ballard WP et al. Phase II trial of 9-Aminocamptothecin administered as a 72-hour continuous infusion in metastatic colorectal carcinoma. *J Clin Oncol* 1997;15:2905-2909.[[Abstract](#)]
46. Saltz LB, Kemeny NE, Tong W et al. 9-Aminocamptothecin by 72-hour continuous intravenous infusion is inactive in the treatment of patients with 5-fluorouracil-refractory colorectal cancer. *Cancer* 1997;80:1727-1732.[[Medline](#)]
47. Verschraegen CF, Natelson EA, Giovanella BC et al. A phase I clinical and pharmacological study of oral 9-nitrocamptothecin, a novel water-insoluble topoisomerase I inhibitor. *Anticancer Drugs* 1998;9:36-44.[[Medline](#)]
48. Bollag G, McCormick F. Regulators and effectors of ras proteins. *Annu Rev Cell Dev Biol* 1991;7:601-632.
49. Liu M, Bryant MS, Chen J et al. Antitumor activity of SCH 66336, an orally bioavailable tricyclic inhibitor of farnesyl protein transferase, in human tumor xenograft models and wap-ras transgenic mice. *Cancer Res* 1998;58:4947-4956.[[Abstract](#)]
50. Hurwitz HI, Colvin OM, Petros WP et al. Phase I and pharmacokinetic study of SCH 66336, a novel FPTI, using a 2-week on, 2-week off schedule. *Proc Am Soc Clin Oncol* 1999;18:599a.
51. Eskens E, Awada A, Verweij J et al. Phase I and pharmacologic study of continuous daily oral SCH 66336, a novel farnesyl transferase inhibitor in patients with solid tumors. *Proc Am Soc Clin Oncol* 1999;18:600a.
52. Awada A, Eskens F, Piccart MJ et al. A clinical and pharmacokinetic study of SCH 66336(SCH) an oral inhibitor of the enzyme farnesyl transferase given once daily in patients with solid tumors. *Clin Cancer Res* 1999;5(suppl):S3733.
53. Skrzat S, Angibaud P, Venet M et al. R115777, a novel imidazole farnesyl transferase inhibitor (FTI) with potent oral antitumor activity. *Proc Am Assoc Cancer Res* 1998;39:2170a.
54. Hudes GR, Schol J, Baab J et al. Phase I clinical and pharmacologic trial of the farnesylation inhibitor R115777 on a 21-day dosing schedule. *Proc Am Soc Clin Oncol* 1999;18:601a.
55. Zujewski J, Horak ID, Bol CJ et al. A phase I and pharmacokinetic study of farnesyl protein transferase inhibitor R115777, in advanced cancer. *J Clin Oncol* 2000;18:927.[[Abstract/Full](#)]

Text]

56. Peeters M, Van Cutsem E, Marse H et al. Phase-I combination trial of the **farnesyltransferase** inhibitor (FTI) R115777 with a 5FU/LV regimen in advanced colorectal (CRC) or pancreatic cancer (PC). Proc Am Soc Clin Oncol 1999;18:858a.
57. Okuda H, Ogura K, Kato A et al. A possible mechanism of eighteen patient deaths caused by interactions of sorivudine, a new antiviral drug, with oral 5-fluorouracil prodrugs. J Pharmacol Exp Ther 1998;287:791-799.[[Abstract/Full Text](#)]
58. Wakisaka S, Shimauchi M, Kaji Y et al. Acute phenytoin intoxication associated with the antineoplastic agent UFT. Fukuoka Igaku Zasshi 1990;81:192-196.[[Medline](#)]
59. Douillard JY, Cunningham D, Roth AD et al. A randomized phase III trial comparing irinotecan+5FU/folinic acid (FA) to the same schedule of 5FU/FA in patients with metastatic colorectal cancer (MCRC) as front-line chemotherapy. Proc Am Soc Clin Oncol 1999;18:899a.
60. Saltz LB, Locker PK, Elfring GL et al. Weekly irinotecan (CPT-11), leucovorin (LV) and fluorouracil (FU) is superior to daily X 5 LV/FU in patients with previously untreated colorectal cancer (CRC). Proc Am Soc Clin Oncol 1999;18:898a.
61. Van Cutsem E, Szanto J, Roth A et al. Evaluation of the addition of oxaliplatin to the same mayo or german 5-FU regimen in advanced refractory colorectal cancer. Proc Am Soc Clin Oncol 1999;18:900a.
62. Feliu J, Calvillo J, Escribano A et al. Neoadjuvant therapy of rectal carcinoma with UFT-folinic acid (LV) plus radiotherapy. Proc Am Soc Clin Oncol 1999;18:917a.
63. Lokich JJ, Moore CL, Anderson NR. Comparison of costs for infusion versus bolus chemotherapy administration: analysis of five standard chemotherapy regimens in three common tumors—Part one. Cancer 1996;78:294-299.[[Medline](#)]
64. Lokich JJ, Moore CL, Anderson NR. Comparisons of costs of infusion versus bolus chemotherapy administration—Part two. Cancer 1996;78:300-303.[[Medline](#)]
65. Liu G, Franssen E, Fitch MI et al. Patient preferences for oral versus intravenous palliative chemotherapy. J Clin Oncol 1997;15:110-115.[[Abstract](#)]
66. Saltz LB, Leichman CG, Young CW et al. A fixed-ratio combination of uracil and Ftorafur (UFT) with low dose leucovorin. An active oral regimen for advanced colorectal cancer. Cancer 1995;75:782-785.[[Medline](#)]
67. Sanchiz F, Milla A. Tegafur-uracil (UFT) plus folinic acid in advanced rectal cancer. Jpn J Clin Oncol 1994;24:322-326.[[Medline](#)]
68. Gonzalez-Baron M, Feliu J, Garcia Giron C et al. UFT modulated with leucovorin in advanced colorectal cancer: Oncopaz experience. Oncology 1997;54(suppl 1):24-29.[[Medline](#)]
69. 1999 Drug Topics—Red Book. Montvale, NJ: Medical Economics Company, 1999.

Received January 21, 2000; accepted for publication March 3, 2000.

This article has been cited by other articles:

- Rose, W. C., Long, B. H., Fairchild, C. R., Lee, F. Y. F., Kadow, J. F. (2001). Preclinical Pharmacology of BMS-275183, an Orally Active Taxane. *Clin Cancer Res* 7: 2016-2021 [[Abstract](#)] [[Full Text](#)]

- ▶ [Abstract of this Article](#)
- ▶ [Reprint \(PDF\) Version of this Article](#)
- ▶ Similar articles found in:
[The Oncologist Online](#)
[PubMed](#)
- ▶ [PubMed Citation](#)
- ▶ This Article has been cited by:
- ▶ Search Medline for articles by:
[Sharma, S.](#) || [Saltz, L. B.](#)
- ▶ [Download to Citation Manager](#)

THE ONCOLOGIST

STEM CELLS

CME

ALPHAMED PRESS JOURNALS

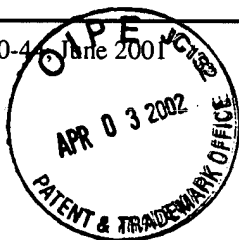
get the journal delivered to your
 **mailbox!**

T
R
Y

STEM CELLS

HOME HELP FEEDBACK SUBSCRIPTIONS ARCHIVE SEARCH SEARCH RESULT

The Oncologist, Vol. 6, Suppl 3, 40-46 June 2001
 © 2001 AlphaMed Press



SUPPLEMENT

Novel Compounds in the Therapy of Breast Cancer: Opportunities for Integration with Docetaxel

Anthony W. Tolcher

Institute of Drug Development, Cancer Therapy Research Center, San Antonio, Texas, USA

Correspondence: Anthony W. Tolcher, M.D., Institute of Drug Development, Cancer Therapy Research Center, 8122 Datapoint, Suite 250, San Antonio, Texas 78229, USA. Telephone: 210-616-5914; Fax: 210-949-5009; e-mail: atolcher@saci.org.

- ▶ [Abstract of this Article](#)
- ▶ [Reprint \(PDF\) Version of this Article](#)
- ▶ Similar articles found in:
 [The Oncologist Online](#)
 [PubMed](#)
- ▶ [PubMed Citation](#)
- ▶ Search Medline for articles by:
 [Tolcher, A. W.](#)
- ▶ [Download to Citation Manager](#)

► ABSTRACT

Increasingly, novel agents are being developed specifically at inhibition of growth factor receptors and events within the signal transduction pathway. These agents include the epidermal growth factor tyrosine kinase inhibitors, the farnesyl transferase inhibitors, and bcl-2 antisense oligonucleotides. Along with these new approaches to molecular targeting, it will be necessary to develop new study designs for drug evaluation. Target validation in both normal surrogate tissues and tumor tissue becomes increasingly relevant in early clinical trials. Furthermore, antitumor efficacy may no longer correlate with normal hematological or nonhematological toxicity, and it may be more appropriate in phase I trials to identify the maximum target inhibition dose rather than the maximum tolerated dose. Moreover, measures of cytoreduction, such as complete and partial response, may be less relevant than disease stabilization for some of these novel agents which have limited cytotoxic effects and would be considered cytostatic agents. Assessment of single-agent activity and the future role in conjunction with cytostatic agents represents the single most important challenge facing the clinical development of these molecular targeted therapies.

Key Words: Tyrosine kinase inhibitors· Farnesyl transferase inhibitors· bcl-2 antisense oligonucleotides· Docetaxel

- ▲ [Top](#)
- [Abstract](#)
- ▼ [Introduction](#)
- ▼ [Agents Targeted at the...](#)
- ▼ [Farnesyl Transferase Inhibitors](#)
- ▼ [Antisense Oligonucleotides](#)
- ▼ [Discussion](#)
- ▼ [References](#)

► INTRODUCTION

Several major new classes of agent are now emerging from phase I/II study. The epidermal growth factor receptor tyrosine kinase inhibitors are the focus of considerable current interest based on the critical role members of the HER family have in cellular proliferation in some tumors. Although, enthusiasm for the farnesyl transferase inhibitors has waxed and waned over the past several years, single-agent antitumor activity has now been observed and has directed development in tumors where inhibition of signal transduction appears to yield antitumor activity, such as breast cancer. Finally, antisense oligonucleotides directed to the bcl-2 gene also may hold promise.

- ▲ [Top](#)
- ▲ [Abstract](#)
- [Introduction](#)
- ▼ [Agents Targeted at the...](#)
- ▼ [Farnesyl Transferase Inhibitors](#)
- ▼ [Antisense Oligonucleotides](#)
- ▼ [Discussion](#)
- ▼ [References](#)

► AGENTS TARGETED AT THE EPIDERMAL GROWTH FACTOR RECEPTOR

The epidermal growth factor receptor (EGFR) is an important target in cancer therapy [1-4]. The EGFR family includes HER-1 (EGFR-1), HER-2, HER-3, and HER-4, and these are expressed in combination in most epithelial-based receptor cells. Activation of these receptors by ligand binding or overexpression leads to phosphorylation of the cytoplasmic ATP binding domain and activates the mitogen-activated proliferation kinase pathway of the signal transduction pathways. From this family of receptors, *HER-2 neu* has been the prototype in breast cancer [5-8]. Overexpression of *HER-2* by gene amplification in breast cancer tumors leads to constitutively activated tyrosine kinase activity, increased cellular proliferation, and a poor clinical outcome. EGFR-1 and the role of cellular proliferation represents an emerging target in many disorders [9].

- ▲ [Top](#)
- ▲ [Abstract](#)
- ▲ [Introduction](#)
- [Agents Targeted at the...](#)
- ▼ [Farnesyl Transferase Inhibitors](#)
- ▼ [Antisense Oligonucleotides](#)
- ▼ [Discussion](#)
- ▼ [References](#)

Members of the EGFR family can be targeted either through the use of specific antibodies, Herceptin being the first such agent, or through the use of more recently developed small molecules which inhibit tyrosine kinase (TK) [10-17]. The humanized monoclonal antibody IMC-C225 directed at EGFR-1 is currently further along in development. This high-affinity antibody is directed to the cysteine-rich domains of the EGFR where it blocks ligand-induced TK activity, inhibiting activation of the MAP kinase pathway [18-21]. This results in decreased cell cycle traverse and potentiation of apoptosis. In addition, inhibition of EGFR may also inhibit the angiogenic growth factors and potentiate effects of both radiation and chemotherapy [22].

The development of C225, however, has to some extent been eclipsed by EGFR tyrosine kinase inhibitors, which are directed toward the tyrosine kinase function of the EGF receptor. EGFR TK inhibitors bind to the ATP binding site on the internal membrane of EGFR. The agents undergoing clinical development include the reversible inhibitors of ZD 1839 (which are highly specific for EGFR-1) and OSI 358,774 [23, 24]. The latter agent is now in phase II study, while ZD 1839 has moved directly to phase III trial in non-small-cell lung cancer.

A second generation of EGFR TK inhibitors has been designed to have a broader spectrum of antitumor activity and to target a wider range of the *erbB* family. Thus, they inhibit not only EGFR-1 but also *HER-2 neu*, for example. Of these irreversible inhibitors, CI-1033 (a *pan-erbB* inhibitor) is now completing phase I evaluation, and EKB 569 (which inhibits both *erbB* 1 and 2) has recently entered phase I study [25, 26]. If these agents prove fully effective and are developed, they may supplant the use of Herceptin.

Both tumor and normal surrogate tissue have been obtained to validate target inhibition of these agents. Preliminary evidence suggests that EGFR phosphorylation can be effectively inhibited in tissue specimens at clinically achievable doses [27].

► FARNESYL TRANSFERASE INHIBITORS

The cascade of signal transduction events that follows activation of the growth factor receptor offers a host of potential targets for intervention. One target of particular current interest is *ras* and its modification [28]. A compulsory step in *ras* protein activation includes the addition of hydrophobic moieties so that it can associate with the internal membrane of the cell [29, 30]. The rate-limiting step in this process is the activity of farnesyl transferase. If this process is inhibited, *ras* can no longer associate with the membrane [31-33]. Inhibiting *ras* protein action, in turn, blocks a number of signal transduction pathways [34-36].

- ▲ [Top](#)
- ▲ [Abstract](#)
- ▲ [Introduction](#)
- ▲ [Agents Targeted at the...](#)
 - [Farnesyl Transferase Inhibitors](#)
- ▼ [Antisense Oligonucleotides](#)
- ▼ [Discussion](#)
- ▼ [References](#)

Several farnesyl transferase inhibitors (FTIs) are in clinical development. They include the orally bioavailable agents R115777 and SCH 66336 and the oral and i.v. agent BMS 214662 [37-39]. The earlier agent, L778123, is no longer in clinical studies.

Although such agents were initially synthesized to specifically target *ras*, particularly in malignancies in which *ras* mutations are prominent, they also inhibit proliferation of cell lines such as MCF-7 which do not have *ras* mutations. These results suggest that FTIs may have a greater spectrum of antiproliferation effect.

Furthermore, in xenograft models, the FT inhibitor R115777, inhibits tumor growth in cell lines which express wild-type rather than mutated *ras* [40].

The FTI R115777 also has clinically important single-agent antitumor activity in breast cancer. In a recently reported phase II study, patients with advanced metastatic breast cancer who were refractory to chemotherapy or hormone therapy were treated with R115777 [41]. Although certain patients experienced neutropenia and thrombocytopenia at 400 mg p.o. b.i.d. dose, subsequent treatment with 300 mg b.i.d. was tolerable and was the phase II dose for most of the patients treated. Three patients (12+%) had partial responses and a further nine (35%) manifested stable disease at 3 months. Although the response rate seen may not appear impressive at initial inspection, by analogy with the development

of Herceptin, it should be possible to determine the characteristics of responding patients and appropriately direct therapy to those patients who may respond. The FTIs may block the downstream pathway of Herceptin and represent an alternative therapeutic strategy in breast cancer. Furthermore, the FTIs may prove to have a broader spectrum of activity against targets in the signal transduction pathway. Combinations of agents that target *HER* family tyrosine kinases and downstream signal transduction elements may in the future overcome resistance to Herceptin.

Evidence to date suggests that the FTIs may act in synergy with the taxanes but not with other classes of cytotoxic drugs [42]. In two phase I studies about to recruit patients, R115777 will be combined with either paclitaxel or docetaxel. An NCI-sponsored study of R115777 with Herceptin is actively accruing patients, and the natural development will include a taxane, FTI, and Herceptin.

The agents considered so far have acted at a variety of points within the growth factor receptor *ras* MAP kinase pathway (Fig. 1[Ⓜ]). In addition, agents now in phase I development target the PI 3 kinase pathway, and hence represent another element in the molecular processes that underlie proliferation. One can envision specific targeting of tumors based on the specific signal transduction pathway used for proliferation.

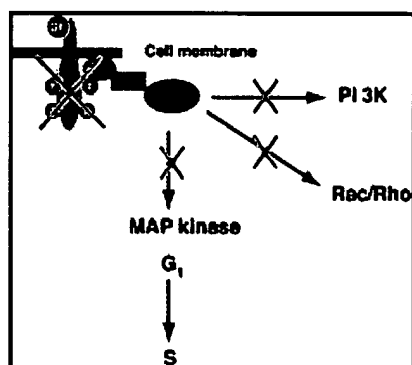


Figure 1. Ras signaling pathway.

[View larger version \(16K\):](#)

[\[in this window\]](#)

[\[in a new window\]](#)

► ANTISENSE OLIGONUCLEOTIDES

Reducing cell proliferation is one element in the therapy of cancer. Predisposing tumor cells to undergo apoptosis is an intervention intended to tip the other side of the balance in a favorable direction. In this process, the *bcl* gene is a clear target. This gene is overexpressed in several malignancies, including prostate, breast, colon carcinomas, melanoma, and some lymphomas [43-45].

Overexpression may also confer resistance to cytotoxic chemotherapy and irradiation. Downregulation

- ▲ [Top](#)
- ▲ [Abstract](#)
- ▲ [Introduction](#)
- ▲ [Agents Targeted at the...](#)
- ▲ [Farnesyl Transferase Inhibitors](#)
 - [Antisense Oligonucleotides](#)
- ▼ [Discussion](#)
- ▼ [References](#)

of bcl-2 protein expression may therefore enhance the efficacy of antitumor agents.

Antisense oligonucleotides are small strands of nucleotides complementary to certain portions of mRNA which degrade mRNA in a sequence-specific manner [46, 47]. G1319, a drug under development which targets *bcl-2*, hybridizes with the first six codons of *bcl-2* mRNA [48, 49]. This leads to ribonuclease digestion of the mRNA and subsequent downregulation of the protein. In certain models, this is sufficient to lead to apoptosis; in other models, *bcl-2* downregulation enhances the antitumor effect of several chemotherapy agents (Fig. 2) [50-53].

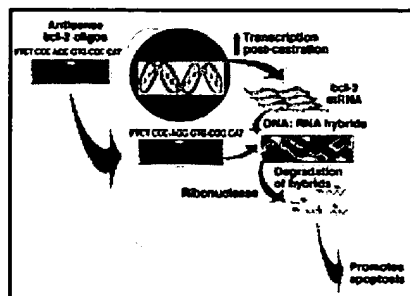


Figure 2. Antisense oligonucleotides degrade mRNA in a sequence-specific manner.

View larger version (60K):

[\[in this window\]](#)

[\[in a new window\]](#)

Based on preclinical models, *Miyake et al.* and others have demonstrated that downregulation of bcl-2 with G3139 acts synergistically with docetaxel, enhancing tumor cell kill [54]. Given these data, *Chen et al.* have embarked on a clinical investigation of weekly docetaxel in combination with G3139 in patients with breast cancer. The antisense oligonucleotide is also being studied in San Antonio in conjunction with docetaxel administered every 3 weeks.

► DISCUSSION

It is now recognized that agents such as those discussed above have both direct effects on a molecular target and indirect effects through inhibition of downstream events, including those involved in signal transduction.

In an attempt to more thoroughly evaluate the effects of agents directed to molecular targets, surrogate measures of biological effects are increasingly being incorporated into phase I studies alongside pharmacological parameters. The importance of these correlative studies is exemplified by the absence of conventional antitumor activity expected with antiproliferative and cytostatic agents.

Increasingly, traditional phase I studies using dose escalation to maximum tolerated dose may no longer

- ▲ [Top](#)
- ▲ [Abstract](#)
- ▲ [Introduction](#)
- ▲ [Agents Targeted at the...](#)
- ▲ [Farnesyl Transferase Inhibitors](#)
- ▲ [Antisense Oligonucleotides](#)
 - [Discussion](#)
 - ▼ [References](#)

be considered appropriate with these agents. More relevant would be studies in which there is escalation to a maximum target-inhibiting dose or a biologically relevant dose.

With conventional cytotoxic agents, increasing efficacy against the tumor target has been so closely correlated with increasing toxicity that the latter has prevented achievement of the optimal antitumor dose. With the novel agents, it may be possible to achieve antitumor activity at doses far lower than would cause significant toxicity (Fig. 3[Ⓢ]). If this proves to be true, the means used for assessing new anticancer agents will have to be fundamentally reassessed with study designs incorporating both toxicity assessment and target validation.

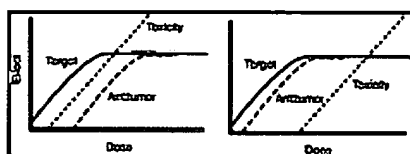


Figure 3. Idealized dose-effect curves for novel agents.

View larger version (9K):

[\[in this window\]](#)

[\[in a new window\]](#)

While demonstration of tumor regression is still an essential step in the development of traditional cytotoxic agents, this may no longer be appropriate for novel agents. Given their reduced toxicity, demonstration that they delay tumor growth may be sufficient to justify their clinical trial, particularly in combination (Fig. 4[Ⓢ]). If this is seen to be the case, there will be a move from the classical measures of cytoreduction such as complete and partial response to time to progression and time to treatment failure, as appropriate measures of an agent's utility prior to evaluating the gold standard endpoint—survival (Fig. 5[Ⓢ]).

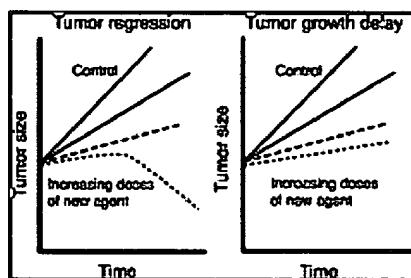


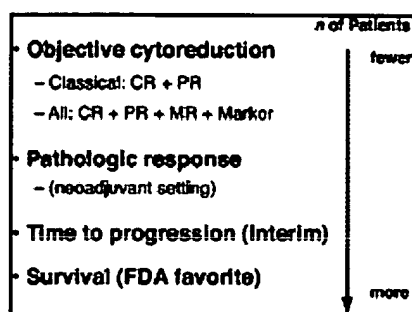
Figure 4. Patterns of antitumor effects.

View larger version (20K):

[\[in this window\]](#)

[\[in a new window\]](#)

Figure 5. Beyond phase I: screening for efficacy. CR = complete response, PR = partial response; MR = moderate



response.

View larger version (22K):

[\[in this window\]](#)[\[in a new window\]](#)

REFERENCES

1. Coussens L, Yang-Feng TL, Liao Y-C et al. Tyrosine kinase receptor with extensive homology to EGF receptor shares chromosomal location with *neu* oncogene. *Science* 1985;230:1132-1139.[[Medline](#)]
2. Bargmann CI, Hung MC, Weinberg RA. The *neu* oncogene encodes an epidermal growth factor receptor-related protein. *Nature* 1986;319:226-230.[[Medline](#)]
3. Akiyama T, Sudo C, Ogawara H et al. The product of the *c-erbB-2* gene: a 185-kilodalton glycoprotein with tyrosine kinase activity. *Science* 1986;232:1644-1646.[[Medline](#)]
4. Popescu NC, King CR, Kraus MH. Localization of the human *cerb-2* gene on normal and rearranged chromosomes 17 to bands q12-21.32. *Genomics* 1989;4:362-366.[[Medline](#)]
5. van de Vijver MJ, Peterse JL, Mooi MJ et al. *Neu*-protein overexpression in breast cancer. Association with comedo-type ductal carcinoma in situ and limited prognostic value in stage II breast cancer. *N Engl J Med* 1988;319:1239-1245.[[Abstract](#)]
6. Slamon DJ, Clark GM, Wong SG et al. Human breast cancer: correlation of relapse and survival with amplification of the *Her-2/neu* oncogene. *Science* 1987;235:177-182.[[Medline](#)]
7. Slamon DJ, Godolphin W, Jones LA et al. Studies of the *HER-2/neu* proto-oncogene in human breast and ovarian cancer. *Science* 1989;244:707-712.[[Medline](#)]
8. Schroeder W, Biesterfeld S, Zillesen S et al. Epidermal growth factor receptor-immunohistochemical detection and clinical significance for the treatment of primary breast cancer. *Anticancer Res* 1997;17:2799-2802.[[Medline](#)]
9. Pinkas-Kramarski R, Shelly M, Guarino BC et al. ErbB tyrosine kinase and the two neuregulin families constitute a ligand-receptor network. *Mol Cell Biol* 1998;18:6090-6101.[[Abstract/Full Text](#)]
10. Carter P, Presta L, Gorman CM et al. Humanization of an anti-p185^{HER} antibody for human cancer therapy. *Proc Natl Acad Sci USA* 1992;89:4285-4289.[[Abstract](#)]
11. Harthwell IM, Wels W, Schlegel J et al. Monoclonal antibodies directed to the *erbB-2* receptor inhibit in vivo tumor cell growth. *Br J Cancer* 1993;68:1140-1145.[[Medline](#)]
12. Drebin JA, Link VC, Greene MI. Monoclonal antibodies reactive with distinct domains of the *neu* oncogene-encoded p185 molecule exert synergistic anti-tumor effects in vivo. *Oncogene* 1988;2:273-277.[[Medline](#)]

- ▲ [Top](#)
- ▲ [Abstract](#)
- ▲ [Introduction](#)
- ▲ [Agents Targeted at the...](#)
- ▲ [Farnesyl Transferase Inhibitors](#)
- ▲ [Antisense Oligonucleotides](#)
- ▲ [Discussion](#)
- [References](#)

13. Drebin JA, Link VC, Greene MI. Monoclonal antibodies specific for the *neu* oncogene product directly mediate anti-tumor effects in vivo. *Oncogene* 1988;2:387-394.[[Medline](#)]
14. Pietras RJ, Pegram MD, Finn RS et al. Remission of human breast cancer xenografts on therapy with humanized monoclonal antibody to HER-2 receptor and DNA-reactive drugs. *Oncogene* 1998;17:2235-2249.[[Medline](#)]
15. Pegram M, Hsu S, Lewis G et al. Inhibitory effects of combinations of HER-2/neu antibody and chemotherapeutic agents used for the treatment of human breast cancer. *Oncogene* 1999;18:2241-2251.[[Medline](#)]
16. Cobleigh MA, Vogel CL, Tripathy D et al. Efficacy and safety of Herceptin (humanized anti-HER2 antibody) as a single agent in 222 women with HER2 overexpression who relapsed following chemotherapy for metastatic breast cancer. *Proc Am Soc Clin Oncol* 1998;17:97a.
17. Slamon D, Leyland-Jones B, Shak S et al. Addition of Herceptin (humanized anti-HER2 antibody) to first line chemotherapy for HER2 overexpressing metastatic breast cancer (HER2⁺/MBC) markedly increases activity: a randomised, multinational controlled phase III trial. *Proc Am Soc Clin Oncol* 1998;17:98a.
18. van der Geer P, Hunter T, Lindberg RA. Receptor protein-tyrosine kinases and their signal transduction pathways. *Annu Rev Cell Biol* 1994;10:251-337.[[Medline](#)]
19. Pinkas-Kramarski R, Soussan L, Waterman H et al. Diversification of Neu differentiation factors and epidermal growth factor signalling by combinatorial receptor interactions. *EMBO J* 1996;15:2452-2467.[[Abstract](#)]
20. Tzahar E, Waterman H, Chen X et al. A hierarchical network of interreceptor interactions determines signal transduction by Neu differentiation factor/neuregulins and epidermal growth factor. *Mol Cell Biol* 1996;16:5276-5287.[[Abstract](#)]
21. Burden S, Yarden Y. Neuregulins and their receptors: a versatile signalling module in organogenesis and oncogenesis. *Neuron* 1997;18:847-855.[[Medline](#)]
22. Baselga J, Norton L, Albanell J et al. Recombinant humanized anti-HER2 antibody (Herceptin) enhances the antitumor activity of paclitaxel and doxorubicin against HER2/*neu* over-expressing human breast cancer xenografts. *Cancer Res* 1998;58:2825-2831.[[Abstract](#)]
23. Ciardiello F, Caputo R, Bianco R et al. Antitumor effect and potentiation of cytotoxic drug activity in human cancer cells by ZD-1839 (Iressa), an epidermal growth factor receptor-selective tyrosine kinase inhibitor. *Clin Cancer Res* 2000;6:2053-2063.[[Abstract/Full Text](#)]
24. Akaza H, Aiba K, Isonishi S et al. Development of molecular targeting drugs for the treatment of cancer-therapeutic potential and issues to be addressed in global development. *Gan To Kagaku Ryoho* 2000;27:1681-1693.[[Medline](#)]
25. Rao GS, Murray S, Ethier SP. Radiosensitization of human breast cancer cells by a novel ErbB family receptor tyrosine kinase inhibitor. *Int J Radiat Oncol Biol Phys* 2000;48:1519-1528. [[Medline](#)]
26. Torrance CJ, Jackson PE, Montgomery E et al. Combinatorial chemoprevention of intestinal neoplasia. *Nat Med* 2000;6:1024-1028.[[Medline](#)]
27. Hammond L, Ranson M, Ferry D et al. ZD1839, an oral epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor: first phase 1, pharmacokinetic (PK) results in patients. *Proc Am Soc Clin Oncol* 1999;18:1500a.
28. Kloog Y, Cox AD, Sinensky M. Concepts in Ras-directed therapy. *Expert Opin Investig Drugs* 1999;8:2121-2140.[[Medline](#)]
29. Downward J. Control of ras activation. *Cancer Surv* 1996;27:87-100.[[Medline](#)]
30. Bollag G, McCormick F. GTPase activating proteins. *Semin Cancer Biol* 1992;3:199-208. [[Medline](#)]
31. Kohl NE. Farnesyltransferase inhibitors. Preclinical development. *Ann NY Acad Sci* 1999;886:91-102. [[Medline](#)]
32. Klooog Y, Cox AD. RAS inhibitors: potential for cancer therapeutics. *Mol Med Today* 2000;6:398-402.[[Medline](#)]

33. Ayllon V, Rebollo A. Ras-induced cellular events [review]. *Mol Membr Biol* 2000;17:65-73. [[Medline](#)]
34. Prendergast GC. Farnesyltransferase inhibitors: antineoplastic mechanism and clinical prospects. *Curr Opin Cell Biol* 2000;12:166-173. [[Medline](#)]
35. Sebti SM, Hamilton AD. Farnesyltransferase and geranylgeranyltransferase I inhibitors in cancer therapy: important mechanistic and bench to bedside issues. *Expert Opin Investig Drugs* 2000;9:2767-2782. [[Medline](#)]
36. Tamanoi F. Inhibitors of Ras farnesyltransferases. *Trends Biochem Sci* 1993;18:349-353. [[Medline](#)]
37. Ashar HR, James L, Gray K et al. The farnesyl transferase inhibitor SCH 66336 induces a G(2) → M or G(1) pause in sensitive human tumor cell lines. *Exp Cell Res* 2001;262:17-27. [[Medline](#)]
38. Adjei AA, Erlichman C, Davis JN et al. A phase I trial of the farnesyl transferase inhibitor SCH66336: evidence for biological and clinical activity. *Cancer Res* 2000;60:1871-1877. [[Abstract/Full Text](#)]
39. Njoroge FG, Taveras AG, Kelly J et al. (+)-4-[2-[4-(8-Chloro-3,10-dibromo-6,11-dihydro-5H-benzo[5, 6]cyclohepta[1,2-b]-pyridin-11(R)-yl)-1-piperidinyl]-2-oxo-ethyl]-1-piperidinecarboxamide (SCH-66336): a very potent farnesyl protein transferase inhibitor as a novel antitumor agent. *J Med Chem* 1998;41:4890-4902. [[Medline](#)]
40. Zujewski J, Horak ID, Bol CJ et al. Phase I and pharmacokinetic study of farnesyl protein transferase inhibitor R115777 in advanced cancer. *J Clin Oncol* 2000;18:927-941. [[Abstract/Full Text](#)]
41. Johnston SR, Ellis PA, Houston S et al. A phase II study of the farnesyl transferase inhibitor R115777 in patients with advanced breast cancer. *Proc Am Soc Clin Oncol* 2000;19:318a.
42. Moasser MM, Sepp-Lorenzino L, Kohl NE et al. Farnesyl transferase inhibitors cause enhanced mitotic sensitivity to Taxol and epothilones. *Proc Natl Acad Sci USA* 1998;95:1369-1374. [[Abstract/Full Text](#)]
43. Gao G, Dou QP. G(1) phase-dependent expression of bcl-2 mRNA and protein correlates with chemoresistance of human cancer cells. *Mol Pharmacol* 2000;58:1001-1010. [[Abstract/Full Text](#)]
44. Thomas A, Giesler T, White E. p53 mediates bcl-2 phosphorylation and apoptosis via activation of the Cdc42/JNK1 pathway. *Oncogene* 2000;19:5259-5269. [[Medline](#)]
45. Pataer A, Smythe WR, Yu R et al. Adenovirus-mediated Bak gene transfer induces apoptosis in mesothelioma cell lines. *J Thorac Cardiovasc Surg* 2001;121:61-67. [[Medline](#)]
46. Faria M, Spiller DG, Dubertret C et al. Phosphoramidate oligonucleotides as potent antisense molecules in cells and in vivo. *Nat Biotechnol* 2001;19:40-44. [[Medline](#)]
47. Lavelle F. New anticancer molecules: drugs for tomorrow? *Bull Cancer* 1999;86:91-95. [[Medline](#)]
48. Gleave ME, Miyake H, Goldie J et al. Targeting bcl-2 gene to delay androgen-independent progression and enhance chemosensitivity in prostate cancer using antisense bcl-2 oligodeoxynucleotides. *Urology* 1999;54(suppl 6A):36-46. [[Medline](#)]
49. Miyake H, Tolcher A, Gleave ME. Antisense Bcl-2 oligodeoxynucleotides inhibit progression to androgen-independence after castration in the Shionogi tumor model. *Cancer Res* 1999;59:4030-4034. [[Abstract/Full Text](#)]
50. Reed JC. Promise and problems of Bcl-2 antisense therapy. *J Natl Cancer Inst* 1997;89:988-990. [[Medline](#)]
51. Campbell MJ, Dawson M, Koeffler HP. Growth inhibition of DU-145 prostate cancer cells by a Bcl-2 antisense oligonucleotide is enhanced by N-(2-hydroxyphenyl)all-trans Retinamide. *Br J Cancer* 1998;77:739-744. [[Medline](#)]
52. Miyake H, Monia BP, Gleave ME. Inhibition of progression to androgen-independence by combined adjuvant treatment with antisense BCL-XL and antisense Bcl-2 oligonucleotides plus Taxol after castration in the Shionogi tumor model. *Int J Cancer* 2000;86:855-862. [[Medline](#)]
53. Miyake H, Tolcher A, Gleave ME. Chemosensitization and delayed androgen-independent recurrence of prostate cancer with the use of antisense Bcl-2 oligodeoxynucleotides. *J Natl Cancer*

Inst 2000;92:34-41.[[Abstract/Full Text](#)]

54. Chen HX, Marshall JL, Trocky N et al. A phase I study of bcl-2 antisense G3139 (GENTA) and weekly docetaxel in patients with advanced breast cancer and other solid tumors. Proc Am Soc Clin Oncol 2000;19:692a.

Received February 6, 2001; accepted for publication March 8, 2001.

[▶ Abstract of this Article](#)
[▶ Reprint \(PDF\) Version of this Article](#)
[▶ Similar articles found in:](#)
[The Oncologist Online](#)
[PubMed](#)
[▶ PubMed Citation](#)
[▶ Search Medline for articles by:](#)
[Tolcher, A. W.](#)
[▶ Download to Citation Manager](#)

[HOME](#) [HELP](#) [FEEDBACK](#) [SUBSCRIPTIONS](#) [ARCHIVE](#) [SEARCH](#) [SEARCH RESULT](#)
[THE ONCOLOGIST](#) [STEM CELLS](#) [CME](#) [ALPHAMED PRESS JOURNALS](#)

